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OF

THE NEW YORK ACADEMY OF MEDICINE

MAY, 1931

INCORPORATED 1851

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ANNUAL GRADUATE FORTNIGHT

BACTERIOPHAGE AS A TREATMENT IN ACUTE MEDICAL AND SURGICAL INFECTIONS*

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Bacon has said "To rule nature man must obey her" and, although this aphorism applies to all science, it is the biologist especially who must always keep this statement in mind. In the physical sciences the investigator is largely without the power of choice, he must obey natural laws. A competent astronomer or an able physicist cannot conduct bad experiments. A physical problem can always be expressed by an equation where all of the terms are real. This is not true for the biologist and for the immunologist in particular. A great many believe, and among them the most experienced, that just as soon as one has made an experiment one is upon the solid ground of experimental science which can not be false. Unfortunately this is not true. The biologist may choose the factors which enter into the equation of each of the problems confronting him. If he disobeys the laws of nature, that is to say, if he adopts unreal conditions, all of the results to which these will lead will be unreal and purely imaginary. It is only when operating under natural conditions that he may hope to find the true solution, and through this be placed in a position to command nature.

*Delivered October 28, 1930.

Let us consider a particular case—that of the phenomenon of recovery from infectious disease. We know, through common experience, that certain species of animals are completely refractory to certain diseases which decimate other species. No one has ever seen, for example, in the course of the most terrible epidemic, a single rabbit contract cholera or a single guinea pig contract typhoid, although men were dying by thousands. The guinea pig and the rabbit, as indeed are all other animals, are refractory to these two diseases. They enjoy a natural immunity.

We know, likewise, by common experience, that a great many of the infectious diseases do not recur or, at least, recur but rarely. It is unusual for a man who has recovered from an attack of typhoid, for example, to contract this disease a second time. A first attack of an immunizing disease leads, therefore, within the individual, to the appearance of a new character. He enjoys an acquired immunity. This immunity, very strong at the beginning, gradually diminishes at a rate more or less rapid in accordance with the disease causing it. In certain cases it disappears completely after a greater or less length of time.

There is, in addition, a third type of immunity. In certain of the chronic diseases such as tuberculosis or syphilis it is very evident that the patient does not enjoy an acquired immunity since the pathogenic organisms continue to develop within the lesions, but he possesses, nevertheless, a new character for reinfection can not occur as long as he remains the carrier of the specific germs. This immunity, certainly different from acquired immunity since it ceases at the moment when the specific organism disappears from the lesion, may be termed pathogenic immunity or, better, symbiotic immunity.

It is only natural a priori to consider the phenomenon of recovery as being within the limits of immunity, but this has yet to be experimentally proved. It is somewhat curious to note that this question of recovery in infectious diseases, a question which would seem fundamental, has always been passed over in silence. Everyone has implicitly

admitted that recovery was a natural consequence of the acquisition of immunity. The reason for this conclusion can readily be understood for all present day immunology is founded upon laboratory experiments carried out with guinea pigs and with rabbits. These animals have been inoculated with cultures of different bacteria, cholera vibrios, typhoid bacilli and others for which these animals possess an absolute natural resistance. In them there have been produced artificial infections which bear no relationship with natural diseases. It is in this way that nature has been disobeyed for such studies can only lead to an imaginary solution. Today immunology is but a pseudo-experimental science.

In so far as recovery is concerned, a simple observation of the facts suggests the hypothesis that this phenomenon can not be the consequence of an acquired immunity. As a matter of fact all of the infectious diseases are not immunizing. Not to mention the pyogenic infections—it is certain that bacillary dysentery can recur at frequent intervals and that the relapses are often as serious, if not more serious, than the initial attack. As for cholera, it is not rare to see recurrences, and all authors of the nineteenth century who have witnessed epidemics in Europe have been unanimous in considering cholera as a non-immunizing disease. On the other hand, with those diseases which are actually immunizing, if recovery results from the acquisition of immunity, how are we to explain satisfactorily the relapses which take place during convalescence, at the moment when the immunity should be at its maximum potency?

These observations suggest the hypothesis that recovery can take place without the phenomena of immunity intervening, and that acquired immunity must be a delayed result of the recovery. In order to verify this hypothesis suggested by observation, it is necessary naturally to study that which takes place within the patient at the moment of recovery, and to do this by adopting an experimental method which conforms to the principle of obeying nature.

It is necessary to study the man or the animal afflicted with natural disease to see the phenomena which take place within him at the time of recovery and throughout the course of convalescence. This method is the only one which can provide a true solution to the problem.

From the beginning of my study of bacteriophagy I have been struck by the fact that the appearance within the body of the patient of the principle which leads to bacteriophagy coincides with the time when the symptoms ameliorate. Absent during the disease, bacteriophage appears constantly in convalescents. Bacteriophagy is thus contemporaneous with recovery. In vitro bacteriophagy consists of the following:

Let us take a few drops of stool derived from a convalescent from bacillary dysentery. Let us emulsify this in about 20 c.c. of sterile bouillon and filter it through a porous porcelain filter, such as the Chamberland, or through a silica candle such as the Berkefeld. Let us add to a young bouillon culture of the dysentery bacillus a drop of this filtrate, and place the tube in the incubator. At first the bouillon appears cloudy, but after a few hours we note that it becomes more and more clear, and, finally after about 12 hours, sometimes more quickly, it becomes perfectly limpid. At this time all of the bacilli are dissolved.

Let us take, then, a new, fresh culture of dysentery bacilli and add to it a drop of the limpid fluid which remains after the disappearance of the bacilli from the first mixture. Let us place this second tube in the incubator. We will find that the phenomenon repeats itself, for after a few hours all of the bacilli are again dissolved and the liquid is clear. We may then remove a drop of the second dissolved culture and introduce it into a third culture of dysentery bacilli. Once more the phenomenon of dissolution takes place.

One might in this manner continue the passages indefinitely, introducing into each new, fresh culture of dysen-

tery bacilli a drop of the preceding one after all of the bacilli have been dissolved. Far from diminishing in intensity in proportion to the degree of dilution of the initial drop of filtrate the phenomenon becomes, on the contrary, more intense. Thus it is that after more than a thousand successive passages I have been able to obtain the complete dissolution of the 2,000 million bacilli contained in 10 c.c. of bouillon, by adding the infinitesimal quantity of a billionth of a cubic centimeter of the preceding dissolved culture.

Such experiments demonstrate that the principle which destroys the bacteria, and to which I have given the name "Bacteriophage," reproduces itself in the course of its action. The phenomenon of bacteriophagy consists essentially, then, in a dissolution of bacteria under the influence of a principle which reproduces; the latter phenomenon, that is, reproduction, being directly related to the bacteria which are dissolved.

Various questions now arise. Is this bacteriophage found only by chance in the intestinal tract of certain dysentery patients, or is it a constant phenomenon? We will return to this question later. Is the phenomenon of bacteriophagy limited to the dysentery bacillus? I have been able to establish the fact that bacteriophagy is a general phenomenon. It has been possible to isolate races of bacteriophage leading to the dissolution of bacteria belonging to very varied species, such as *Eberthella dysenteriae, paradysenteriae, typhi, paratyphi,* and *sanguinaria; Escherichia coli; Salmonella schotmülleri, pullora, suipestifer,* and *typhi-murium; Proteus vulgaris; Vibrio comma; Pasteurella pestis,* and *bovis; Cornybacterium diphtheriae;* and *B. subtilis.* Other investigators have isolated bacteriophage races active with staphylococci, streptococci, and pneumococci, and even with bacteria parasitic of plants, such as *Rhizobium radicicolum, B. tumefaciens,* and *B. carotovorus.* The diversity of the bacteria attacked warrants the belief that the phenomenon is, indeed, general, perhaps involving all bacteria.

Various experiments show that the bacteriophage exists in corpuscular form. One such experiment, the most simple, consists in adding to 10 c.c. of a well-grown bacterial culture an infinitesimal trace, a billionth of a cubic centimeter, of a filtrate containing active bacteriophage. If a drop of this culture is spread immediately on agar we will obtain, after incubation, a growth of bacterial culture over the surface of the media, and this will be spotted with circular bare areas which appear to be perfectly sterile and are visible to the naked eye. Each of these plaques represents a colony of bacteriophage made up of millions of corpuscles, all the issue of a single corpuscle deposited on the agar at the time of spreading. Each corpuscle has commenced to multiply at the expense of the neighboring bacteria. The destruction of the bacteria and the simultaneous multiplication of bacteriophage corpuscles is so active that after a few hours the area of destruction is so wide as to be visible to the unaided eye.

For lack of time I will not discuss all of the characteristics of the bacteriophage phenomenon for it is in reality extremely complex. I will restrict myself to some of the essential ideas. The bacteriophage corpuscle is a living, ultramicroscopic being as is proved by the fact that this corpuscle dissolves bacteria through the agency of a ferment which it secretes. The secretion of a ferment implies a metabolism and this is an essential character of living beings. A bacteriophage is, therefore, of necessity a virus, a parasite of bacteria.

In its action each bacteriophage is not specific, for a given bacteriophage may parasitize and dissolve bacteria belonging to different species, sometimes as unrelated as the streptococcus and the colon bacillus or even the plague bacillus and *B. typhosus*. The characters of each strain of bacteriophage are variable. There are races of bacteriophage able to attack many species of bacteria, others which attack but a single species or even but a single bacterial strain. Certain of them are so potent that they are able in vitro to destroy and to dissolve within less than two hours

all of the bacteria contained in a culture, while others exercise but a scarcely perceptible, partial action.

Adaptability is an exclusive property of living beings and the bacteriophage possesses this character to a very high degree. There are, however, in this respect differences between different races for certain bacteriophages adapt themselves very readily, while others do so very slowly. In so far as the present discussion is concerned, the most important character of adaptability is represented by the faculty which each strain of bacteriophage possesses of adapting itself to the parasitism of new bacterial species which heretofore were not attacked. This experiment of adaptation can even be effected in vitro. It is possible, for example, to adapt a bacteriophage which originally, at the time of isolation, was active only upon *B. coli* to the parasitism of *B. typhosus*. This property of adaptation is rapidly lost in races of bacteriophage maintained under laboratory conditions.

There is another important consideration. When attacked by a powerful bacteriophage the bacterium succumbs, but if the potency of the bacteriophage is less the bacterium is capable of resistance, in which case it then contracts a true chronic disease accompanied by profound modifications in its characters. With regard to the subject now under discussion the most important of these modifications involves the variation in bacterial virulence, and this is usually attenuated and may completely disappear.

In brief, these are the principal characters of the very complex phenomenon of bacteriophagy.

We have seen that the principle which causes bacteriophagy can be uniformly isolated from the convalescent and we are able to conclude that bacteriophagy in vivo is contemporaneous with recovery. Is it the cause?

In the first place let us state that the bacteriophage virus does not appear spontaneously at the moment of recovery. Experiment demonstrates that the bacteriophage exists in the intestinal content of all healthy individuals where it

grows at the expense of the saprophytic bacteria, of *B. coli* in particular, which are daily ingested with the food. Thanks to its faculty of adaptation, the normal intestinal bacteriophage becomes able to parasitize foreign bacteria which may become implanted, not only within the intestines but in any organ whatsoever, for experiment shows that the bacteriophage passes readily into the circulation.

In order to prove if the bacteriophage is really the cause of a recovery it is only necessary to study patients affected with acute infectious diseases from the beginning of the disease up until the end of convalescence. This is what I have done for various human and animal diseases. Here is, in summary, what I have observed. The condition of the patient depends upon the behavior of the bacteriophage and recovery takes place only when the destroying potency of the bacteriophage reaches an intensity sufficient to lead to the bacteriophagy of the pathogenic bacteria.

I am not able, for lack of time, to describe the many studies which I have made upon this subject during different epidemics in Europe, in Indo-China, and in India. Here are, as an example, the results of the studies made upon cholera. These results are expressed in the form of curves, with the solid line representing the severity of the disease as determined by the different symptoms; 10 represents the maximum severity where all of the symptoms are present to the highest degree, 0 indicates the absence of symptoms, that is, recovery. The dotted line presents the curve of potency of the bacteriophage isolated from the patient at the same time in its action upon the cholera vibrio. Between 10 and 6 on the scale tests of potency in vitro show that there is a complete bacteriophagy in a time varying from 2½ hours (10) to 12 hours (6), below 6 the bacteriophagy is only partial, becoming less as the coefficient drops; 0 represents no activity upon the cholera vibrio.

As may be seen from these curves, not only is the phenomenon of recovery strictly related to the behavior of the bacteriophage, but the condition of the patient at a given

moment is always a function of the activity of the bacteriophage. If bacteriophagy does not take place the patient dies.

In bacillary dysentery, in typhoid and the paratyphoid fevers, in different animal septicemias, and in human and murine plague the examination of patients reveals the same relationship between recovery and bacteriophagy in vivo.

It is necessary, however, to emphasize the fact that the phenomenon of bacteriophagy in vivo is far more complex than that occurring in vitro. In the latter case only two beings are involved, the bacterium and its parasite, the bacteriophage. In vivo a third factor enters; the host. In my first book on bacteriophage published in 1921, I described experiments which tend to show that opsonins are in reality the lysins secreted by the bacteriophage corpuscles during bacteriophagy. Let us take two tubes containing like mixtures of sensitive bacteria and leukocytes and let us add to one of these tubes a suspension of bacteriophage or a solution of lysin freed from bacteriophage corpuscles. We will find that phagocytosis is from five to fifty times more active in the presence of the lysin than it is in the control tube. The opsonic power of bacteriophage has since been confirmed by various investigators, including Gohs and Jocobsohn, Weiss and Arnold, Nelson, and Smith.

Thus opsonic action tends naturally to prevent the formation of secondary cultures which are so frequent in vitro, but even though these may be formed, a third phenomenon intervenes which also depends entirely upon the bacteriophage. I have stated above that bacteria which resist the action of bacteriophage undergo modifications in their characters and principally in that of their virulence, which generally becomes attenuated and often disappears completely. This it is easy to prove experimentally.

Three distinct phenomena, therefore, take place in vivo. Bacteriophagy itself, a powerful opsonic action, and an at-

tenuation in the virulence of the pathogenic bacteria. These three phenomena are induced by bacteriophage and all three contribute toward recovery.

All these studies tend therefore to show that recovery is in no way derived from a phenomenon of immunity as had been believed up to the present time, but rather that it is a direct result of bacteriophage in vivo. It is, furthermore, easy to prove this conclusion for it may be done by means of crossed experiments. It is possible, easy indeed, to introduce into a culture of the pathogenic bacterium a trace of a suspension of a virulent bacteriophage, the bacteria are attacked and destroyed, and meanwhile the bacteriophage multiplies. That which was at the beginning a culture of bacteria becomes, after a few hours, a culture of bacteriophage. Let us give a patient by mouth, at the onset of symptoms, a few drops of this culture of bacteriophage. Bacteriophagy must take place in vivo and recovery must follow. The patient will not be forced to take the chance of his own intestinal bacteriophage undergoing an adaptation, for we can inaugurate at the beginning of the disease, the natural processes of recovery.

I will state briefly what has been done up to the present time in this direction. From 1919 on I have made experiments upon patients affected with bacillary dysentery, causing each patient to ingest two cubic centimeters of a culture of bacteriophage having a high virulence for dysentery bacilli. In all cases, without exception, all of the morbid symptoms disappeared within a few hours, in from four to twenty according to the case, and the next day the patient was definitely convalescent. Since that time this method of treatment has been applied on a large scale, principally in the Soudan and in Brazil.

In Brazil, as the result of control experiments conducted by da Costa Cruz, who obtained results identical with those which I had reported, the Oswalde Cruz Institute of the Brazilian Government has prepared, since 1924, cultures of a highly virulent bacteriophage for the dysentery bacilli. These have been placed in two cubic centimeter ampules

and distributed to hospitals, to government health officers, and to all physicians who have requested them. This mode of treatment has quickly supplanted all others, including the use of antidysenteric serum, which has been abandoned. The results obained in the first 10,000 cases have been published and only two failures are recorded.

As for the Soudan, this phrase, summarizing the results, appears in a letter of the Director of the Medical Service. "The results of treatment of bacillary dysentery with it have been little short of miraculous." A single failure, the case of an infant already moribund when brought into the hospital, occurred among several hundred cases treated.

In the year 1927 while in India, as the result of the experiments of which I have spoken, I attempted the treatment of Asiatic cholera. These attempts at therapy were made in the Punjab, on the natives cared for in their homes and to whom no other medication was given. Each patient received an initial dose of two cubic centimeters of a virulent bacteriophage, and with the family a second dose of four cubic centimeters diluted in one hundred cubic centimeters of water was left with instructions to give it to the patient by spoonfuls during the three or four hours following. I should state that I merely furnished the cultures of bacteriophage, treatment was carried out by Major Malone of the Indian Medical Service, assisted by the other officers of the Service. As it was impossible to enforce any one mode of treatment, the family of the patient was free to accept or refuse it, in the latter case usually resorting to the prescriptions of the Hindoo medicine man. The majority of the patients for whom authorization was granted were found in a critical state; indeed, it was only because of this that parents, despairing of saving them, accepted the new treatment. As a control series we have taken those cases in which the bacteriophage treatment was refused. In spite of these extremely unfavorable conditions the mortality in the controls was 62.9 per cent, and among those treated with bacteriophage 8.1 per cent.

Since then Colonel Morison of the Indian Medical Ser-

vice has applied the same mode of treatment in epidemics of cholera in Assam and working also in the villages he has obtained comparable results, the mortality varying from 8 to 11 per cent among the treated while the mortality among those not treated by bacteriophage varied from 60 to more than 80 per cent according to the epidemic.

Asheshov has treated patients in the hospital by applying bacteriophage treatment by the intravenous route and he has succeeded in lowering the mortality to about 2 per cent.

Let us pass to another disease which has a high mortality and which has furnished the most striking results. In 1926 while in Egypt I treated four cases of bubonic plague by injection of the bacteriophage into the buboes; all four of the patients recovered.

In the course of an epidemic which occurred in Senegal, Dr. Couvy, Director of the School of Medicine at Dakar, faced with the non-effectiveness of antiplague serum in severe cases of the disease, attempted the treatment by bacteriophage, utilizing a strain isolated from a convalescent. In order to ascertain in a definite manner the value of this treatment he applied it solely to cases of extreme severity in whom death seemed to be certain within a short time. "Either they appeared moribund after failure of the serum treatment, or it was given at once to patients whose condition appeared desperate" as he states in his paper. Among such patients the mortality is practically one hundred per cent, but with bacteriophage treatment he obtained 15 recoveries among the 21 cases treated. In the course of this epidemic 8 cases of septicemic plague were treated by serum before the trial of bacteriophage. All of these died. Two cases treated by bacteriophage recovered in spite of the fact that the bacilli were so abundant in the blood that they could be disclosed by direct microscopic examination. Of nine cases of pneumonic plague treated by serum all died (as is well known, pneumonic plague is without exception fatal) while one case treated with bacteriophage recovered.

"The action of bacteriophage" states Couvy "manifests itself by an abrupt fall in the temperature, often the defervescence is violent, a fall of several degrees. The general condition rapidly improves. The antitoxic action is most sharp and the hallucinations quickly give place to calm. The periadenitis disappears, the buboes regress, and convalescence takes place within a few days. One never sees the interminable suppurations so frequent with other methods of treatment. There is no necrosis or gangrene."

Let us state in passing that the antitoxic action manifested so quickly and effectively by the bacteriophage is absolutely clear cut, although it is difficult to explain in the present state of our knowledge. I have observed it not only in plague but in other toxic diseases which I have treated with bacteriophage, cholera and bacillary dysentery among others.

Let us pass on to other diseases having a high mortality. We know that recovery is rare in staphylococcus septicemia, the mortality being about 90 per cent. In 1929, at my suggestion, Dr. Davioud treated a hopeless case in the following manner. Five cubic centimeters of a suspension of staphylococcus bacteriophage was diluted in 500 c.c. of physiological saline. This was all introduced intravenously, the period of injection occupying about one hour. This is, indeed, the technic which I have recommended for all intravenous injections of bacteriophage, and it is possible to inject in this manner without danger of immediate shock as much as 25 c.c. of a suspension of bacteriophage. Two hours after the injection there occurred a strong thermic reaction with chills. Upon the morning of the next day the temperature was normal and convalescence began. Eight days later the patient left the hospital, recovered. When seen ten months later she had enjoyed perfect health. Since then many other cases of staphylococcus septicemia have been treated in the same manner in the hospitals of Paris with a like degree of success.

Dutton, the first I believe, has treated with success cases of streptococcus septicemia, and Raiga has very recently

treated this condition. Since here defervescence has not taken place as quickly after the injection as in the preceding cases, upon my advice he made a series of ten intramuscular injections of 5 c.c. each with an interval of 20 hours between each injection. Here is an example. A woman of 28 years, with a puerperal infection was treated simultaneously with septicemine, pyoformine, immunotransfusion, fixation abscesses, and antistreptococcus serum. On the third of July, confronted with the failure of all these methods and by the fact that the patient was gravely ill, the physician in charge requested Dr. Raiga to apply bacteriophage. The temperature was then 41° C. He gave an intravenous injection of 10 c.c. of streptobacteriophage diluted in 500 c.c. of physiological saline. No reaction followed. In spite of the fact that the temperature continued during the following day to vary between 40 and 41° and the blood cultures remained positive, the condition of the patient improved and the appetite returned. Since two injections of antistreptococcus serum had been made in the two flanks there had developed in these regions a diffuse ligneous phlegmon. On the right the infiltration had progressed toward the anterior region of the thigh and had assumed the appearance of a gangrenous phlegmon. Purulent fistulae extended to the knee. On the 18th of July a series of 10 daily intramuscular injections of 5 c.c. of streptococcus bacteriophage were commenced. On the 23rd of July the slough was removed. Upon the 31st of July the blood culture became negative and the temperature progressively lower. The patient left the hospital, cured, on the 31st of August.

Let us turn to still another type of disease—typhoid fever. Since 1923 many papers have appeared upon the subject of its treatment by bacteriophage. Some of them (Hauduroy, Alessandrini, and Doria among others) reported excellent results, while with others (Wolff, for example) the results were negative. I believe, however, that I have recently discovered the cause of these differences. I will speak of them shortly when I consider the general conditions governing treatment by bacteriophage.

For two years I have studied this question and have made experiments in many centers in France. One experiment involving about 150 cases shows that if one administers by mouth a suspension of bacteriophage (I have used a mixture containing many strains of typhoid bacteriophage and several strains of coli bacteriophage) in a dose of 2 c.c. repeated every four hours, one does not obtain a cure in the strict sense of the word, but the disease develops in the form of a simple fever without complications. The stools are formed and normal, the patient does not complain of any disturbance and regains his appetite. None of these cases have died.

On the other hand, when one applies bacteriophage by the intravenous route in the manner indicated above one induces in about half of these cases a strong thermic reaction with chills followed by a rapid fall in the temperature which reaches normal in 48 hours. In the other half of the cases no reaction takes place and the disease follows its normal course.

In view of these remarks, and it is in this direction that I intend to continue my studies, it would seem that an intravenous injection of typhoid bacteriophage might be given, continuing the treatment in the cases where the salutary reaction does not take place, either by administration by mouth as in the first series of cases mentioned, or by serial intramuscular injections such as those used in the streptococcus septicemias.

In infantile diarrheas I have applied treatment by bacteriophage in several hundred cases, using a mixture containing a large number of races of bacteriophage active upon the different pathogenic bacilli which may be found in the intestines of patients—dysentery bacilli of the Flexner or Hiss types, Morgan bacilli, and *B. proteus*. Bacteriophage is administered by mouth in doses of 2 c.c., this being repeated every two hours until the stools have become normal. The effect is usually very prompt and in more than 80 per cent of the cases recovery is obtained within 24 hours. The results would certainly be still much

more favorable if new strains of bacteriophage were added, for it seems that infantile diarrhea is not a definite entity from the standpoint of etiology, but that it may be caused by bacteria of various types. By using a mixture containing bacteriophage capable of acting upon all of those bacteria which cause infantile diarrhea one might hope to be successful in 100 per cent of cases. This appears the more probable, since I have found that the efficiency of the treatment increases as new races of bacteriophage are added to the preparation used for the treatment of this disease.

I will only mention here the treatment of urinary infections due to colon bacilli, for a great many authors have studied this problem and have published their results. It may be said that in acute infections prompt recovery is the rule following intravesicular injections of coli bacteriophage active for the colon bacillus causing the disease. It must also be said that recovery is the rule in these infections whatever the treatment employed. In chronic cases a review of the results indicates that about 60 per cent of the cases recover when treated by instillation into the bladder in conjunction with a series of subcutaneous or intramuscular injections. This figure is raised to about 85 per cent if the instillations are made, not into the bladder, but into the pelvis of the kidney involved. It should be added that it has not yet been possible to isolate strains of bacteriophage acting upon all the cultures of coli which may be found in chronic cases. In a given case of chronic infection caused by this organism it is first essential to determine whether the bacillus of the patient is attacked by a stock bacteriophage. If it is not, it is essential to utilize an "autobacteriophage." This difficulty is not present in other diseases, for with the exception of B. coli races, we now possess strains of bacteriophage which are polyvalent.

Bacteriophage treatment of staphylococcus infections has been very extensively applied. Since the general principle of the method consists in placing the bacteriophage in as intimate a contact as is possible with the pathogenic

bacterium it is essential in staphylococcus infections to inject directly into the focus. Since such injections may often be very painful one may, as Jaquemaire has shown, mix with the staphylobacteriophage a quantity of a suitable anesthetic, novocaine for example. This treatment has up to the present been applied in thousands of cases. For example, Raiga alone has reported the results of this treatment on more than 1,000 different cases, Churman Rices 300 cases. The series of Larkum is very large, and Halphen has used the treatment in 600 cases of tonsillar abscesses, etc. Other types of staphylococcus infection have been treated with equal success, such as furunculosis, carbuncles, paronychia, abscesses of all kinds, of the gums, of the breast, and rectal abscesses. It has been used in phlegmons, in infected wounds, and in osteomyelitis. All investigators who have used this mode of treatment in these different infections are unanimous in stating that the results obtained are far superior to those secured with other methods. This is especially true as regards the rapidity of the action and the absence of scars, which of course are very significant in connection with lesions of the face. One interesting fact recorded by several authors and which I have observed upon several occasions is that very quickly after the first injection of bacteriophage into the pyogenic focus the painfulness disappears completely. The patient who, prior to the intervention, was continually moaning, after one or two hours experienced a sensation of euphoria. This action is especially striking in the case of certain very painful abscesses, those involving the anal region for example. This is not a specific action in particular patients, but is a general effect.

One other type of infection should be mentioned briefly, that is, the treatment of chronic bronchitis, of angina, and of coryza by means of a mixture of different races of bacteriophage active for those organisms which may be isolated from the throat in these conditions. The bacteriophage is here applied by spraying the nose and the throat. I have seen the results in about 300 cases of these different conditions treated in this way and in from 60 to 70 per

cent recovery was rapid. As is the case for other diseases in which the specific germ varies, the results would certainly be improved with the addition of new strains of bacteriophage to the stock.

I must end this lecture in which, for lack of time, I have been forced merely to cite facts without entering into the details of each particular case, with a few general considerations.

Treatment by bacteriophage has been, I believe, demonstrated to be the specific treatment *par excellence*, since it leads to recovery through a mechanism identical with that of natural recovery. Because of its nature one may hope to obtain results only when the bacteriophage administered is endowed with a maximum potency against the pathogenic organism involved. As we have seen, it is possible to isolate very powerful races of bacteriophage, other races are less active and in some the action is very weak indeed. Any attempt at treatment with any type of bacteriophage of low potency is to court a certain defeat. The *sine qua non* of success is the utilization of bacteriophage races selected with care.

I would add a second statement, one which is equally important. I have recently discovered that the therapeutic effect of a bacteriophage is the stronger the more recently the bacteriophage has been isolated. After a series of cultures in the laboratory, and although in vitro the virulence of the bacteriophage is maintained intact, it loses more or less quickly its power of acting in vivo. Preliminary studies already indicate that this attenuation of in vivo action is due to the fact that gradually, as cultivation continues, the bacteriophage loses the faculty of adaptation. In plague, for example, this attenuating behavior is so marked that after four or five laboratory passages the bacteriophage has lost all therapeutic action. Nevertheless, this same race, tested in vitro, shows no weakening in its ability to attack plague bacilli. The same facts have been noted in cholera, and it is probably true also for typhoid fever. With the staphylococcus bacteriophage, on

the contrary, it would seem that the therapeutic action may be maintained for a very long time through passages in vitro. This attenuation of action in vivo is caused by the passages in vitro, and is not due to the period of preservation, for a bacteriophage which has undergone but two or three of these passages and is then preserved in sealed ampules retains its properties intact for many months or even for several years.

A third observation may be made. Whatever the disease under consideration the bacteriophage must be administered in such a way that it can quickly come into contact within the body with the bacteria which it is designed to destroy. This condition can always be readily met, since one has only to select the mode of administration suited to each particular case. The question of posology is of no very great importance, since the bacteriophage commences to multiply just as soon as it comes into contact with susceptible bacteria. Theoretically a billionth of a drop should suffice provided the bacteriophage corpuscles are placed in contact with the bacteria which they are to destroy. In vitro this fact is readily demonstrated, but it is not the same in vivo. However, since the bacteriophage has no action upon the cells of the body and since, as a result of this, it is possible to administer an unlimited quantity without inconvenience to the patient, even if the diagnosis is erroneous, and since it is always desirable to induce a rapid destruction of the pathogenic bacteria, it is in general wise to administer reasonably large doses. In relation to this subject I might state that as a result of laboratory experiments which have been poorly interpreted I have recommended that intramuscular or subcutaneous injections be not repeated. Subsequent experiments have shown that such a statement was not justified and that it is often possible to administer a series of ten or fifteen large doses, that is 5 to 10 c.c. without causing any inconvenience for the patient.

If I may now make a final recommendation, I would say that bacteriophage destined for therapeutic usage should

be prepared in accordance with a proved technic. It should not contain bacteria and it is, indeed, easy to demonstrate whether this condition is fulfilled. Suspensions of bacteriophage are perfectly clear despite the fact that billions of bacteriophage corpuscles are present. The slightest turbidity in an ampule indicates a certain contamination and such material should not be used.

Bacteriophage therapy is still in its infancy and many studies are still necessary before we will learn all the results that we may anticipate, but that which has already been done in many diseases justifies the belief that this is the specific treatment *par excellence* and that it will attain a wider and wider application.

INFECTIONS OF SKIN AND THE SUBCUTANEOUS TISSUE*

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INTRODUCTION

It is with considerable hesitancy that I speak to you this evening on the subject which the chairman has given you; because it is a subject with which every one is familiar and includes conditions which every general practitioner is constantly meeting in his day's work and in which from the earliest stages of his practice, he has had a wealth of experience. Upon every phase of it, all of you will probably have very decided opinions. I feel therefore, that my paper will serve to open a discussion in your minds rather than to present dogmatic opinions. The scope of the topic given to me by Dr. Reynolds makes it necessary for me to cover a fairly wide field but I shall try to deal with general principles rather than with specific details; and these general principles I present from my own personal experience and reflections, from my observations of the methods of other members of the surgical staffs to which I have belonged, and from the experiences of others which have been reported in the literature.

Although the subject of my paper might lead one to expect some treatment of the dermatological features of skin infections, I propose to limit my remarks to the surgical aspects. The acute inflammations of the skin are so often linked up with the deeper invasion of bacteria either into the subcutaneous tissues or into the general circulation that they are generally considered surgical problems, whereas chronic lesions are more apt to be limited to the

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skin itself and are amenable to non-operative therapy. In many instances these cases are trivial and respond to almost any method of treatment, but at times they go from bad to worse in spite of anything the doctor tries to do. They usually take a great deal of his time and attention. He very often considers them a plagued nuisance, requiring his time and attention out of all proportion to the return which they give him, either in professional experience, or in the appreciation of the patients, or in the monetary recompense.

Anatomy

I should like to call to your attention first of all, certain features of the anatomy of the skin as well as the tissues just beneath the skin which are necessary for the understanding of the development and progress of these acute infections, for the anatomy as well as the physiology of the skin affects in no small measure the course of events. The body is covered with an epithelial coat varying in thickness to a considerable degree according to the exposure of the parts, the use to which they are subjected and to the normal movements of the underlying structures. In general those parts which are more exposed to trauma are thick, and those which are more protected are thin. Beside the main creases of the skin, which in general correspond to the bending of the various joints of the body, there are myriads of smaller wrinkles which are apparent with slighter motions. In the depths of these wrinkles the epithelial coat is thin and in these creases bacteria may lodge. The upper layers of the skin are hornified, being made up of dried cells which have gradually been pushed to the surface by the multiplication of living cells in the basal layer of the epidermis. As the cells of the basal layer multiply the more superficial layers are carried farther and farther away from their food supply which comes by way of the intercellular channels in the deeper layers of the epidermis. This outer layer of dead cells offers a very strong barrier to the entrance of microörganisms and if it were not broken by the frequent exit of small

ducts or perforated by hairs it would probably be a much more efficient barrier to infection than it is. In these ducts, however, and in the hair follicles, and in the sebaceous glands which discharge into the hair follicles and in the finer skin crevasses, the bacteria with which the body comes in contact, as it moves about from place to place, may lodge. The chief points to remember with regard to the physiology of the skin are that it is a flexible, elastic, mechanical barrier anointed by the secretion of the sweat and sebaceous glands, and that its blood vessels dilate and contract in response to vasomotor stimuli and in response to the application of heat or cold. These points all play prominent rôles in the process of infection.

Let us now consider the anatomical features of the tissues beneath the skin, which modify the course of an infection. Over most of the body, the subcutaneous tissues consist in a layer of fat and areolar tissue overlying deep fascia and muscle. In certain parts, however, the skin immediately overlies bones, tendon-sheaths and fascial compartments. The most important of these are in the hand and it is of utmost necessity for the surgeon who essays to treat hand infections to know in detail these anatomical structures. Otherwise he will certainly make mistakes which will result in irreparable damage to his patient. Even those who know this region of the body well, find it of great aid to study the books to refresh their memories with the somewhat intricate relationships which are found here, before tackling any of these cases. To mention a few of these important anatomical features, let me call to your mind the perpendicular septa and the fatty compartments of the anterior closed space of the distal phalanx of the finger; the exposure of the tendon sheaths of the fingers just beneath the skin at the middle and distal flexion creases; the canals through which the tendons of the lumbrical muscles pass; the connection of the tendon sheath of the little finger with the ulnar bursa which in the palm and wrist surrounds the tendons of all of the flexor tendons, except those of the thumb; the similar relationship between the tendon sheath of the thumb and the radial

bursa; the limitation of the tendon sheaths of the other fingers at the transverse bend of the hand; the thickness of the skin of the palm resulting so frequently in the collar button type of abscess and lastly the fascial spaces of the palm, deep to the tendons, divided by the transverse adductor muscle of the thumb. The free motion of the fingers in the fine movements of the hands depends upon the free play of the tendons within the sheath, and the small muscles outside.

Pathogenesis

Infections of the skin and subcutaneous tissue arise in two common ways. Organisms invade these regions either from outside or from within the body. Organisms from without may either penetrate through an intact skin or be carried into the deeper tissues through a wound of one sort or another. Invasion from without is by far the commonest cause and the one with which we shall chiefly deal in this paper. Organisms from within may reach these tissues either by direct extension from some deep focus, as for example, from an osteomyelitis or through the circulation as metastases from some other region. These will be more fully considered by other speakers.

"Spontaneous" infections. Let us first consider those infections due to organisms penetrating the body through a seemingly intact skin. When bacteria lodge in the ducts of the sweat or sebaceous glands or skin crevasses, some of them find the environment favorable for their proliferation. As soon as they have begun to metabolize, their secretory or excretory products are discharged into the surrounding medium and may be irritating to the neighboring cells. Organisms are usually quickly washed or rubbed off from the surface of the skin and if they stay for any length of time on the surface, they are not likely to find the conditions of moisture and nourishment satisfactory for growth and multiplication. Even if they were to do so, the horny layer of the skin, in most cases, would resist the irritating action of their products. In the sweat and

sebaceous glands there may be only a few layers of living cells separating the bacteria from the subcutaneous tissues. By continued multiplication the organisms may call forth a leukocytic response which results in a frank formation of pus. The epithelium over the small focus becomes pushed up and the pus shows through a thinned out layer of epithelium, and we call it a pimple or a pustule. I believe that these lesions are almost always due to organisms from without and not due to "bad blood" as the patients so often suppose. I wonder how often this misconception is due to something the doctor has told them? Usually these pustules are very superficial affairs and in the great majority of cases spontaneously resolve; but if this lesion is squeezed or pricked, the organisms frequently invade the deeper tissues. Then the compartments and partitions in the deeper layers of the skin, of which we spoke above, particularly at the back of the neck, on the back and on the dorsal surface of the forearm, play a part in the further progress of the infection. If the bacteria get down beneath the epidermis and into these columns, as they proliferate, their metabolic products cause a liquefaction of the soft tissues between the partitions. This liquefaction permits the organisms to migrate downward in these columns and they follow this line of least resistance until they strike the layer of subcutaneous fascia. Then they spread laterally beneath the partitions and, again following the line of least resistance, spread upward toward the surface in the adjacent columns; at first resulting in extreme swelling due to infiltration of fluid and wandering cells; and later resulting in necrosis of the tissue partly by the direct action of the metabolic products of the bacteria and partly the thrombosis of blood vessels. If the infection limits itself to a single compartment, it remains a furuncle but if it involves neighboring compartments it becomes a carbuncle. In parts of the body where these partitions do not exist or are thin, a single cavity forms and this is called a furuncle if small; or an abscess, if large. The organisms which are able to gain a foothold in the hair follicles or sebaceous glands and sweat ducts are usually

limited to the staphylococcus group. When hemolytic streptococcus enters, it may produce pustules or furuncles, but frequently spreads extensively in the superficial layers of the skin causing the well-known picture of erysipelas. More rarely the anthrax bacillus is the cause of an apparently spontaneous lesion. These organisms may be said, therefore, to penetrate the intact skin.

Infections arising from contaminated wounds. Almost all other organisms which cause infections of the skin and subcutaneous tissues are introduced through a broken skin. This break may be microscopic, but in most cases it is more than that for there is usually a history of a prick, a cut, a scratch, an abrasion or a laceration. If the break goes down to the layers of living cells where body fluids are circulating, the organisms which are introduced immediately find a medium in which certain of them may be able to grow.

In the great majority of cases when cultures are made, infections of the skin and subcutaneous tissues yield a single organism, this would seem to indicate that often only one type of organism, of the many different kinds which are surely introduced whenever a wound is made in the skin, is able to maintain itself against the defences of the body, grow, multiply, and metabolize, while the other organisms do not. This would lead one to believe that in most instances the conditions are not favorable for the great majority of organisms which are introduced and the fact that many wounds heal without infection would also lend weight to this idea. On the other hand with many wounds, particularly those in which there are many foreign bodies in the form of particles of dirt, and in which there is considerable injury to tissue, the conditions are favorable for a large variety of organisms so that more than one type gains a foothold. It is well known that there are certain bacterial synergisms and antagonisms; certain species will not grow together, while others augment one another. In general it may be said that when a wound is infected with two or more different varieties of organ-

isms, the infection is more severe than if only one of these types is represented.

The establishment of bacteria in a wound. Whenever a wound is made, there is an indeterminate number of organisms of different species and inert foreign bodies introduced, but there is also some injury to the tissue cells, some extravasation of blood and lymph and a concomitant injury to the blood vessels supplying the area. It is of interest to speculate upon the course of events which take place when bacteria have passed the primary physical barrier of the surface epithelium and have entered into the deeper tissues. They may have come directly in an actively growing state from another animal or human body, and find themselves in an environment not very different from the one they have just left; or they may have come from an environment entirely different from the one in which they find themselves. Chesney, Burke and many others have studied the question of the viability of organisms and the dormancy of organisms when transferred from one environment to another and have shown that a lag or a dormancy in their development varies with the differences in environment on the one hand, and the differences in the individual organisms, on the other. In general, it may be said that when bacteria, in an actively growing state, are transferred to a similar environment they develop much more rapidly, than if they are not in an actively growing state or are transferred to an entirely different medium. At the same time even from an actively growing culture, when individual organisms are transplanted, some grow out quickly while others lie dormant for a number of days or even weeks. These points are of particular interest in our consideration of the question of the initiation of an infection, when bacteria have gained entrance into the body, and help to explain why it is common for pathologists to become infected from autopsies, or for surgeons to become infected when they prick a finger with a knife or a needle during an operation on a septic case; or for patients to infect themselves, producing series of boils, or carbuncles, over a period of weeks or

months; or for epidemics of infection to spread in hospitals where there is not the most meticulous care in the treatment of infectious cases.

We must first consider from the point of view of the bacteria whether or not they are viable, and if viable whether or not they can adapt themselves to the conditions sufficiently well for them to proliferate and produce toxic products. Certain conditions of temperature, hydrogen-ion concentration, oxidation reduction relationships and nutrient material are necessary for the growth of bacteria and any organisms which survive must not only find conditions favorable but must be able to resist the so-called defensive forces of the body.

Incubation period. When a wound is made and contaminated with bacteria, most of the organisms which are introduced do not find a favorable environment and either lie quiescent or are destroyed. If they survive there is almost always an interval of hours or days before the signs of infection set in. This is called the "period of incubation" of the disease. This depends first of all upon the elaboration of irritating substances arising from the bacteria, from the dead tissue and from the foreign substances which have been introduced; and secondly upon the rapidity with which the body can react to those irritating substances. From the point of view of the bacteria the speed of the inflammatory reaction depends upon the number and virulence of the viable organisms originally introduced, the rapidity of their adaptation and multiplication and the intensity of the irritating quality of their metabolic products. From the point of view of the body, the evidence of inflammation awaits the reaction of the local tissues to the foreign substances which have been introduced or elaborated and the mobilization of the other defensive forces from remoter parts of the body. The speed of the reaction also depends upon the state of relative immunity or susceptibility of the individual to the organisms in question.

Immunity and susceptibility. We know very little

about resistance of the body against such organisms as the streptococcus and staphylococcus. Apparently many of the laws which come into play in the development of immunity to other diseases do not apply to these infections. There is no natural, racial or individual immunity of any importance against these organisms and after an infection, even the local immunity which apparently can be demonstrated, is a transient thing. On the other hand there is considerable clinical data to indicate that these infections often originate at a time when the individual is below his or her normal health. In a few instances these infections occur in patients who are perfectly well but more often, there is a history of exposure to cold, a period of mental or physical strain of one sort or another, or some precedent illness. Streptococcus is notably an organism of secondary invasion which produces many of the serious complications of diseases such as the exanthemata, and it is believed that this is so either because of some adjuvant action which the streptococcus has, when it grows along with some other organism, or else that the individual has lowered his threshold of resistance against the streptococcus. What is the meaning of this lowered resistance? Is it possible to overcome it, either before or after the advent of the infection? Is it possible to measure it? It seems rational to believe that what we call "general health" would affect the immediate defensive factors at the site of entrance of organisms for example, in a contaminated wound, in such diseases as diabetes where the sugar content of the tissues may be increased or in vascular diseases where the nutrition of the tissues is continuously inferior. More important still are those disturbances of general health which interfere with the ability of the body to mobilize the defensive elements coming from other parts of the body. Any illness either acute or chronic may make it less easy for a patient to mobilize his defense at the site of the invading organisms. Cold or hunger may delay it. An instability of the sympathetic nervous system may not only delay the mobilization of the defenses in remote tissues but alter the permeability of the capillaries at the

site of infection rendering it difficult for the leukocytes and other protective substances to pass through the blood vessels and localize at the site of conflict.

Sensitivity. It is well known that in children and to a certain degree in youth up to twenty years, infections may arise in bones or other internal tissues which have no contact with the exterior of the body, without any apparent evidence of an inflammatory reaction to indicate the portal of entry of the organisms. Inasmuch as the causative organisms are generally of the staphylococcus or hemolytic streptococcus groups, the most likely point of entrance is somewhere on the skin or nasopharynx. The explanation which has been offered for this phenomenon is this, that children and youth are not sufficiently sensitized to these organisms to arouse any reaction to their presence when they enter the body. Nevertheless the organisms survive, are picked up in the circulation and are transported to internal tissues. Like other foreign bodies they are picked up by the bone marrow capillaries, spleen, liver and lungs. Some writers have thought that this localization of bacteria is due to some special predilection of certain bacteria for certain tissues. It has even been called a "chemotaxis" of certain tissues for certain organisms. The bacteria are generally destroyed in the lungs, liver, and spleen but in the bone they may be able to gain a foothold and multiply. During the incubation period the body becomes sensitized and at the end of that period, the whole process blossoms forth as an acute infection. In contradistinction to children, adults, being already sensitized, react promptly when the bacteria appear at the portal of entry. This seems to be a plausible explanation in view of certain facts which are now known about the sensitization of individuals to bacteria and their products.

Pathology

Signs and symptoms of inflammation. When bacteria multiply and secrete their metabolic products, certain chemico-physical alterations occur in the surrounding tissues to which the body reacts with certain chemico-

physical changes which give us the well-known picture of inflammation. Redness, pain, swelling and heat develop. The redness is chiefly due to the dilatation of the blood vessels, which we call a local hyperemia. Heat is due chiefly to this increased circulation, but may be also due to some extent to the chemical reactions taking place. The swelling is due to the exudation of fluids and the infiltration and extravasation of cells. The pain is due in part to the swelling but chiefly to the direct action of the inflammatory products on the pain nerve receptors.

The migration of leukocytes and chemotaxis. In the early stages of inflammation one of the most striking phenomena is the localized concentration of polymorphonuclear leukocytes. These have been seen in the process of passing through capillary walls. The process by which they are attracted to the site of irritation is called positive chemotaxis and it is thought to be due to certain surface tension changes resulting from the irritating substances. For it is known that a cell will move in the direction of that portion of its circumference which has the lowest surface tension. The chemotactic influence is most intense at the site of the activity of the organisms and becomes less so as distance increases. A general leukocytosis usually results from a stimulation of polymorphonuclears in the bone marrow, either by a direct action of the chemotactic influences reaching the bone marrow through the circulation or by an indirect action from an initial leukopenia caused by the withdrawal of leukocytes at the site of inflammation from the general circulation. In the later stages of the infection there is a gradual increase in the number of large mononuclear leukocytes which, according to varying opinions, arise from local fixed tissue cells, from the endothelium of blood vessels, from the monocytes of the blood or else reach the part through the general circulation or by direct migration from other sources. Whatever their origin, it is certain that they are found in great numbers in the later stages of almost any infection.

The process of inflammation. After the initial signs of inflammation appear, the course of events depends upon the balance of the forces pitted against one another and the structure of the battleground over which they struggle. The battle may exhibit any degree of intensity. The organisms may proliferate rapidly or slowly. Their metabolic products may act directly on the tissues causing necrosis or they may diffuse widely in the local tissues without destroying them and be carried off into the general circulation causing intoxication of remote tissues or the body as a whole. The capillary system of blood vessels and lymphatics is a closed system. Fluids may pass through the walls, either through or between the cells but bacteria are held on the outside until they are taken up by wandering cells or endothelial cells and carried inside, or until the wall is liquefied and an opening is made. It is probable that before liquefaction of blood vessel walls takes place, thrombi form within. There may be extensive thrombosis of the capillary blood vessels and lymphatics, thus increasing the rapidity of tissue necrosis. Thrombi may spread from the smaller radicles to the large vessels and as liquefaction of the blood vessels themselves takes place, the bacteria heretofore outside of the circulation, find themselves inside, but held for the time being by the clot. They may, however, continue their activity, liquefy the clot and when they have reached the limits of the thrombus be carried off in the blood stream to the heart and thence to distant capillary beds. If they are in masses either because of agglutination or because imbedded in blood clot they are generally caught in the capillaries and are either destroyed or continue to grow forming a metastasis and this in like manner may in turn send out its metastases on the venous side.

The spread of infection. It is interesting to note in autopsy studies of these infections that in some instances the spread of the infection is solely lymphatic and in others solely venous. In still others, to be sure, the spread is both venous and lymphatic but usually one or the other route predominates. This may be accidental but one won-

ders whether or not there is a predilection of certain organisms for certain routes or certain tissues. When bacteria have entered the circulation as individuals, they are rapidly destroyed as Hopkins and Parker and others have shown. These workers injected sublethal and lethal doses of streptococci into rabbits and at frequent intervals thereafter took blood cultures. The number of circulating viable bacteria rapidly diminished and entirely disappeared in the sublethal doses. In the lethal doses also they entirely disappeared for a time but after an interval, reappeared and increased in numbers until death ensued. They found on autopsy in the sublethal cases remnants of bacteria in the capillary endothelium of the lungs, liver, spleen, and bone marrow, and in the lethal cases they invariably found foci of bacterial growth. The increase in bacterial count in the blood stream did not represent an actual growth of organisms in the blood stream but an outpouring of bacteria from these foci in greater numbers than they could be killed off in the circulation. When it is remembered that the blood makes a complete circuit of the body every minute, passing through two or three capillary beds with each circuit and that even under the best of conditions bacteria multiply only once in every fifteen or twenty minutes it is seen that bacteria have to run the gauntlet of the capillary endothelial cells thirty to forty times and be subject to the lethal action of the circulating blood for a considerable length of time. It is probable that not until these defenses are exhausted, in other words not until just before death, do the bacteria in the blood stream multiply. I think that we may safely say that if a septicemia persists, there must be a focus somewhere pouring out bacteria into the blood stream faster than they can be killed off. This is an extremely important fact to keep in mind, in our treatment of these infections.

Cellular resistance to bacterial spread. Some of the tissue cells at the site of the lesion take part in the phagocyting of the bacteria but in the initial stages of the infection the chief activity seems to be on the part of the polymorphonuclear leukocytes. They migrate from blood

vessels, take up bacteria, sometimes destroy them and at other times are destroyed by them either before or after their ingestion. The less resistant bacteria are destroyed and the less resistant cells are destroyed. Here we have a survival of the fittest so that as the bacteria which survive proliferate, the more resistant qualities are propagated from generation to generation. As Welch has said the bacteria develop an immunity to the body and it may be that even within a single generation an organism may develop an increased resistance to the body cells. On the other hand the tissue cells, although they do not proliferate as rapidly as the bacteria, are believed likewise to increase their resistance to the bacteria. As vessels become thrombosed, the way is blocked for the emigration of the leukocytes but where the vessels are patent at the periphery of the lesion they are able to pass through the vessel walls and in this zone are preponderant over the organisms. When infected tissues are stained to show bacteria it is seen that they are present in great numbers where there has been tissue necrosis but in the zone of cellulitis they are relatively few. Here the body cells have the advantage and either spontaneously or with surgical help generally halt the process. However, if the bacteria are able to withstand this defense and continue to proliferate and produce their toxins in spite of it, the tissues break down and the zone of cellulitis advances. It is easy to understand that there may be very little absorption from a central area of necrosis but a great deal from a zone of cellulitis where blood vessels are patent and the circulation of fluids continues. As we have said above in the later stages of an infection an examination of the tissues under the microscope reveals an ever increasing number of large mononuclear phagocytes, clasmatocytes, or histiocytes as they have been called. To these cells we attribute the defense which finally gets the better of the infection and they too are probably responsible in no small measure for the local immunity which persists for a time against reinfection with the same or even with other organisms.

Clinical Variations with Different Organisms

As indicated by the nature of injury. It is of importance for the surgeon to know the organisms causing the infection. At times the site of the lesion and the nature of the injury will enable one to predict, with some degree of certainty, the species of organisms which has been introduced and the type of infection which may develop. For example, the infections which arise following a human bite are known to carry a mixture of mouth organisms which produce a fairly characteristic initiation and course of infection. Lacerated wounds, produced by fragments of shell in war time carrying in clothing and soil, are known to result frequently in an infection with the organisms of the soil and feces—namely, gas-gangrene, tetanus and the like. Infections which develop after operation, particularly where the tissues have been uncontaminated before, are known to yield the organisms which are common in the air or in the nose and throat of the operating personnel when improper masks are worn and either the nose or the mouth is exposed. If peritonitis is present at the time an abdominal wound is made or the gut is opened during the course of a celiotomy, the subcutaneous tissues may become infected by the organisms known to be present in the intestine.

As indicated by the symptoms and signs. The type of organisms may also be frequently prognosticated by the development and course of the early stages of an infection, for example, when local and general symptoms arise within the first twelve or twenty-four hours following a wound, the infection is commonly due to the hemolytic streptococcus. Wound infections which develop more slowly are more likely to be due to the staphylococcus group, and the general symptoms occur later. Staphylococcus infections in general, run true to form, except that they vary considerably in the degree of intoxication and in the rapidity of their development. They are usually characterized by a fairly rapid necrosis of the subcutaneous tissues. The process is usually localized fairly

early and the neighboring tissues are relatively normal. Streptococcus infections on the other hand, usually cause a very rapid development of general intoxication. The process is more diffuse and it spreads rapidly. The surrounding tissues are not normal, but are edematous and red and there is very little destruction of tissue but a marked infiltration of fluid and cells. When such tissues are examined under the microscope, there are seen edema and cellular exudation in which the nuclei of the cells stain sharply with apparently no death of cells or connective tissue. Under certain conditions, however, possibly in hypersensitive individuals, there is a very rapid necrosis of tissue and very rapid thrombosis of blood vessels. This necrosis of tissue in both staphylococcus and streptococcus infections results in a liquefaction of the tissues most involved, and a cavity formation at this site which grows larger as the necrosis spreads outward from the centre. When there is a symbiosis of two or more different varieties of organisms, necrosis may take place when a pure culture of either one would result simply in edema without any necrosis.

Treatment

With the foregoing general principles in mind how shall we treat infections of the skin and subcutaneous tissues? The purpose of the surgeon in his treatment of all of these conditions should be to restore the part to its normal form and function as soon as may be. The ideal result would be a resolution of the part without any evidence of destruction of tissue but more often than not when an infection is well under way the surgeon's knife may be called upon to destroy superficial tissue in order that there may be a cessation of further destruction of the deeper structures.

Prophylactic treatment. Prophylactic measures with regard to those infections which appear to be more or less spontaneous but which arise from organisms entering through hair follicles and sebaceous and sweat glands, consist in frequent washing of the skin with hot water

and soap, particularly after the exposure of the body to known sources of contamination. This especially applies to doctors and nurses who frequently handle infected wounds. The prophylactic treatment of infections which arise in wounds has of course been given great consideration by countless surgeons in times past. This is more important and more difficult than that which we apply to avoid spontaneous infections because of the variability of the depth and extent of the wound and the variety and number of the organisms and other foreign bodies which are introduced into the wound. Our whole surgical aseptic technique is prophylactic against these infections in operative wounds. When wounds have occurred from injury we must assume that organisms have been introduced and from our experience we may estimate to some degree the number and kind if we know the conditions under which the injury took place. The chief prophylactic measure is the removal of these organisms and other foreign bodies from the wound, as completely as possible. Likewise any injured tissue should be excised, which the part can safely spare and which might favor the growth of those bacteria which remain. The former can frequently be carried out to a considerable extent by the patient himself or the lay members of the family, if a doctor is not immediately available; but the doctor must review this preliminary treatment and carry it further if necessary when he arrives. Certain life insurance companies have circularized the public with regard to this important step in the prevention of wound infection and have particularly advocated cleansing rather than using antiseptics for fear too much reliance should be placed upon the latter and the cleansing be neglected. This emphasis on cleansing cannot be too greatly stressed but with the wound as clean as possible, antiseptics may be used and in my experience, Dakin's solution, bichloride of mercury, mercurochrome or iodine locally may be safely and effectively employed. Sometimes the suturing of a wound may be considered a prophylactic measure against infection but this should only be done in tissues well supplied with blood like the face or scalp and

when the wound has been made within an hour after the injury. In any other circumstances, suturing may favor rather than prevent an infection. When the nature of the injury would lead one to suspect the presence of soil organisms the prophylactic use of tetanus or gas-gangrene antitoxin is indicated.

Abortive treatment. When the first signs of infection have appeared, measures should be instituted which may be called abortive. When pimples have developed, and they may do so in a very short time, the measures should be conservative, any manipulation of the parts should be avoided. Picking, scratching, squeezing, are all strongly contra-indicated for we know that if these pimples are left entirely alone, the great majority of them will subside quietly and disappear within three or four days. On the other hand, we know that if they are manipulated, or picked, or squeezed that a large proportion of them will get worse, the infection will spread into the deeper tissues and even in the best of hands will produce serious lesions which take a long time to get well. Furthermore, when pustules are broken the organisms are invariably carried by hands to other parts of the body surface or are rubbed into neighboring pores. When pimples first form, the resolution process may be favored by the use of iodine and if this be painted upon the pimples morning and evening without any manipulation, nine times out of ten, they will dry up with great rapidity. Such resolution is also favored by an erythematous dose of sunshine, ultra-violet light, or X-rays. If the infection has gone beneath the skin into the subcutaneous tissues, the application of iodine, ultra-violet light, or X-rays is in my experience, of little value. Abortive measures in the earliest stages of those infections resulting from contaminated wounds, consists in opening the wound, removing all gross foreign bodies still present, the application of heat or the instillation of Dakin's solution. At times a complete debridement of the area is indicated before heat or antiseptics are used.

Active treatment. With an infection in full swing, the

"spontaneous" skin lesions such as furuncles and carbuncles are best treated by the application of heat and an adequate opening at the proper time. This requires the best judgment of the surgeon. With furuncles the application of heat may result in a resolution and a spontaneous discharge of the necrotic core, but if they do not resolve promptly they should be incised when central fluctuation can be appreciated with the palpating fingers. A crucial incision into a furuncle at that time will usually result in prompt resolution. In certain parts of the body where it is desirable to avoid scarring, as on the face, compromise measures must be adopted. Here an opening may be made painstakingly through the skin with carbolic acid on a toothpick. This opening tends to seal and must be kept patent with grease until the necrotic tissue has entirely liquefied and come away. Usually several applications of carbolic are necessary. With carbuncles, the columns and the partitions which we have mentioned above must be kept in mind. In places where scarring is to be avoided the compromise measures may be applied but the solution of the tough partitions is a slow process even with carbolic and adequate drainage by this means is not always possible. In these cases crucial incision with an undermining of the triangular flaps up to and beyond the margin of induration thus cutting across the partitions and permitting drainage of the superficial and deep layers, will generally result in gradual resolution but the slough is tenacious and its separation must be aided by the application of Dakin's solution. To my mind, the ideal treatment for a carbuncle in those regions where scarring is of little concern, is a complete excision just beyond the margin of induration. Thus the whole infective process is removed from the body leaving relatively normal tissues. The area first enlarges but with the rapid growth of granulation tissue which ensues, after five or six days, the area may be free of all slough and ready for skin grafting. This often cuts in half or in quarter the duration of the illness and the resulting scar is reduced to less than a quarter of the original area removed. Excision is particularly indicated

in diabetics for any other method of treatment is notoriously slow and it is difficult to control the diabetes in the presence of the mass of infected tissue. The use of x-ray or the circum-injection of blood in cases of carbuncles have not proven successful in my hands for they have almost always required subsequent operative treatment and simply served to delay the final cure. With regard to the deeper and more extensive infections, as will be explained below, there are certain groups of cases in which immediate operation is demanded; but, in the majority of cases certain preliminary procedures are of value in order that the recovery may be as prompt and complete as possible. It has been found again and again that too early an operation in a cellulitis in which there is no central necrosis, delays the final resolution of the process, because drainage is inadequate and the release of tension delays the liquefaction of dying tissues. When central necrosis has taken place, the process is usually more limited in extent and the necessary limit for the incision is more clearly defined. At that time the incision gives a maximum drainage with a minimum amount of injury and the release of tension favors the circulation of the tissue which is living and increases the rapidity of its resolution and the separation of the dead walls of the cavity.

The effect of cold and heat. In the early stages of acute inflammation the application of cold, either in the form of a wet dressing or an ice bag with elevation of the part will frequently result in the halting of the progress of the infection and a prompt resolution. On the other hand, cold may not be well tolerated by the patient and I have seen case after case in which application of cold either did not halt the spread of the disease or else maintained it "in statu quo" without either spread or resolution. In such cases I have frequently seen a change to hot applications followed by a rapid resolution or a rapid localization of pus. For that reason, except in the very earliest stages of inflammation I feel that heat is decidedly preferable to cold in the great majority of cases. Heat may be applied by means of a radiating light or an infra-red

lamp, but better still by means of hot wet applications such as poultices or stupes. If the part can be totally immersed in a bath, heat may be effectively applied in this way. The temperature should be well above body temperature but below that which would cause a burn, in other words, somewhere in the neighborhood of 110° F. which is usually well borne. The favorable effect of heat is not clearly understood. We know that the part becomes red and assume that the circulation has been increased, and that this is responsible for the result. Attempts have been made to determine the effect of hot water baths on the innermost portions of a member, and it is found that in the muscle it is almost impossible to raise the temperature more than a degree or two above that of the body. In the subcutaneous tissues, however, the temperature may be raised 5° or 6° above the temperature of the body and be maintained at that degree for an indefinite length of time. Assuming that the optimum temperature for the growth of organisms which infect the human body is the normal temperature of that body, it is not unreasonable to suppose that higher temperatures of even 4° or 5° will be unfavorable to the growth of the organisms. At the same time, the tissues which have been killed, become liquefied more rapidly than they would without the application of heat. And tissues in which there is simple edema and cellular infiltration, return to the normal state more rapidly than if heat were not applied.

Emergency operations. Although on most parts of the body surface it is advisable to delay operation until a considerable amount of necrosis has taken place and fluctuation can be definitely made out on physical examination, there are certain parts of the body and there are certain types of inflammation where this is most undesirable because delay may destroy important structures, favor extensive spread or by edema, block the vital passage ways.

Hand infections. The first of these exceptions is illustrated by tendon sheath and fascial space infections of the

hand. Here, any necrosis of tendons results in such a disabling interference of function, that the best surgical opinion now agrees that a suspected tendon sheath infection demands immediate operation as soon as it is seen by the surgeon. If a tendon sheath which is not infected is opened unnecessarily it does infinitely less harm than if an involved one is allowed to progress for a few hours. In the best of hands, it is only those cases which are operated on within a short time of the onset of the infection which get a good return of function. With the use of a tourniquet, so as to keep the field free from blood, it is possible to cut down upon the tendon sheath, examine it from the outside and determine without opening it, whether or not it contains fluid; if there is no distension of the tendon sheath it may be safely left alone; if it is shown to be distended with fluid it must certainly be opened, and if there has been no necrosis of the tendon sheath, or the tendon, the chances are favorable for a good return of function, provided the proper after-treatment is given. This includes the immersion of hand and forearm in hot sterile boric acid solution at regular intervals with elevation of the part wrapped in a sterile towel in between the baths. When the cellulitis has subsided the wound may be irrigated at frequent intervals with Dakin's solution to remove any sloughs which may be present. Early motion is emphasized and this depends largely upon the coöperation of the patient. Fascial space infections also demand early operation with adequate drainage and similar aftercare, not so much for the danger of the infection per se as for the possible spread to the neighboring tendon sheaths.

Hemolytic streptococcus gangrene. Another condition demanding immediate operation is the so-called hemolytic streptococcus gangrene. This begins very much like an ordinary streptococcus cellulitis, although it is usually very much more rapid and extensive in its development. It may occur on any part of the body, but usually on the extremities; there is redness, swelling, pain, and dysfunction, due chiefly to the increased weight of the edematous member. The margin of the infection is ill defined. It fades

off into normal tissues. There is usually no lymphangiitis or lymphadenitis. On the third, fourth, or fifth day the pathognomonic sign of the disease appears, which is an ill defined but definite dusky discoloration of the skin somewhere near the centre of the lesion, although it may occur in several patches distinct from one another. It is at this time that operation should be done and incision made through the subcutaneous tissues, down to the deep fascia. It will be found that the subcutaneous tissues are filled with a sero-sanguinous fluid and the fat will show an extensive early necrosis which extends far beyond the area of discoloration on the surface. The incision must be carried beyond the limits of the subcutaneous necrosis or the infection will continue to spread. Sometimes multiple incisions have to be made in order to expose this area of subcutaneous necrosis adequately. If incisions are not made when this first blue discoloration appears the gangrene of the subcutaneous tissues spreads extensively within the next few hours and the areas of the discoloration increase in size and produce blisters and bullae, giving the appearance of a bad burn. If it is allowed to progress further, through the destruction of the subcutaneous tissue, the blood culture may become positive, metastases may form in other parts of the body and death may ensue. We do not know the cause of this unusually rapid development of necrosis in these cases; whether it is due to a peculiar quality of the infecting organisms or to the hypersensitive state of the patient.

Ludwig's angina. A third exception to the rule of delayed operation in subcutaneous infections is the group of infections in the region in the neck in which the hemolytic streptococcus and occasionally other organisms, produce a massive dense swelling of the deep tissues under the fascia which, because of its denseness, masks the sign of fluctuation. Here the edema, by spreading towards the larynx and œsophagus may block off the airway or produce dysphagia. Here early incision, even though it does not find a deep abscess cavity relieves tension, offers a certain degree of drainage and frequently prevents or relieves the

edema of the larynx which offers such a real threat to the life of the patient.

Gas-gangrene. Another infection of the subcutaneous tissues demanding immediate operation is gas-gangrene. When the symptoms and signs of this affliction are present —namely, prostration, with rapid pulse, high fever, anxiety and local evidence of a rapid spread of infection, swelling, redness, pain, heat and subcutaneous emphysema, with or without a bronzing of the skin; any delay in operation increases the risk and makes the cure more difficult. These cases need extensive incision, the removal of foreign bodies and necrotic tissue, and prompt administration of large doses of gas-gangrene antitoxin. If the organism has been determined this antitoxin should be specific for the organism in question; but, if it is not possible to determine the organism promptly, a polyvalent antitoxin should be used.

Post-Operative Treatment

After operation the surgeon must continue to use the means at his disposal for the rapid resolution of the process, the separation of the dead tissue, the contraction of the healing tissues and the final closure of the wound. As long as there is any diffuse inflammation, the application of heat is indicated either by poultices, hot water bags, light or by immersing the part in a bath; but, when the cellulitis has completely subsided the removal of the dead tissues is the next most important step. And now the use of Dakin's solution delivered to the site of the necrotic tissue at frequent intervals of time, offers the best means which we now have at our disposal. For the separation of slough where the wounds are deep and the dressings are painful, Dakin's solution may best be delivered by the Carrel tubes. Where the cavity is superficial, it can often best be delivered by the frequent application of compresses wet with the solution; and their removal at frequent intervals has the added advantage of removing the exudate and the liberated pieces of slough. When the slough is entirely separated and granulations are active and bacteriological ex-

amination of the exudate reveals the absence of bacteria both on smear and culture, the wound may be closed. This secondary closure may be done at times in the presence of innocuous organisms, but should never be done if streptococcus is present or other virulent organisms. A flat wound cannot easily be closed secondarily without extensive undermining. Skin grafting is indicated for these wounds and this may be done before there is bacteriological evidence of complete sterilization of the wound, providing that there is evidence of new epithelium already around the margin of the wound, and provided that there is no undermining of the edges of any part of the wound. For if grafting is done when those edges are present, the grafts will not take in the neighborhood of the undermined flaps, but will be digested by the exudate coming from beneath the flaps.

General Treatment

After the proper surgical handling of the infection itself, what measures are there available for building up the general resistance of the patient? I shall consider a few of the important measures that have been tried, namely, transfusion of blood, medication by mouth or vein, diet, ultra-violet light, vaccines and sera.

Transfusions. Blood transfusions are being used more and more in the treatment of infections, but there is no unanimity of opinion with regard to their real virtue, inasmuch as protective antibodies are not present in serum and the relatively small number of leukocytes transferred could not be expected to have any particularly favorable action. While transfusion may have little effect upon the course of the infection it usually makes the patient feel better and may be used. This may be just enough to turn the tide in the patient's favor but we must not expect too much of it as a curative measure. The expense of transfusion at the present day should be kept in mind. In anemic cases resulting from prolonged infection by hemolytic organisms, transfusion is of real value but I have seen transfusion used repeatedly in the acute stages of infection

without any definite improvement in the condition of the patient and certainly transfusion should never be made a substitute for the proper surgical procedure. On the other hand during convalescence, after the acute process is under control, transfusions do a striking amount of good, perhaps helping the patient more than any other form of treatment.

Chemotherapy. The use of medicines in these infections is of very little avail. Tin preparations in staphylococcus infections or copper in streptococcus infections have not yielded the results claimed for them. The "sterilizans magna" so hopefully anticipated by the intravenous use of antiseptic dyes such as mercurochrome, gentian violet, acriflavine and the like, has been tried and found wanting. When given intravenously these dyes are very rapidly diluted in the blood and withdrawn from it by the tissues, so that their concentration in the blood which reaches the focus of infection is far below the concentration necessary to destroy the organisms, unless injected in doses which are toxic to the body as a whole. In fact the organisms at the site of an infection are not approachable by these substances even when they are injected directly into the artery supplying the part which is involved, as Zau and the writer showed. This does not mean, however, that hope should be abandoned in this direction for the time may come when a substance will be found which can be given in such concentration as to affect favorably the course of the infection without injuring the normal cells of the body.

Ultra-violet light and vitamines. In recent years ultra-violet light has been given a great deal of credit for improving the general body resistance. We do not know how it acts, but it seems to have a favorable effect in certain cases. The subject is a relatively new one but it offers an encouraging field of research which in the future will almost certainly rationalize this method of treatment. Still more recently the question of vitamine deficiency, as a predisposing factor to infections, has been given a considerable amount of attention both by clinical and laboratory observers. Vitamine B has been considered the most im-

portant vitamine element necessary to increase the body's resistance to infections. Here again the question has not been settled, but the popular use and abuse of yeast is one of the results of this investigation. It has been said that the normal diet of man has an excess of this vitamine, but, when the patient cannot take a normal diet it is possible to increase to a considerable extent the intake of vitamine B. No harmful effects have been reported as far as I know.

The use of vaccines and sera. On another evening the subject of vaccines and sera will be taken up in more detail but from the point of view of infections of the skin and subcutaneous tissues, I would like to speak briefly of my judgment concerning them. Research workers who have studied streptococcus and staphylococcus have been continually baffled by the weakness of the response of experimental animals to vaccines. Within recent years it has been found that antitoxins may be produced in animals by the injection of toxic filtrates from certain strains, of both streptococcus and staphylococcus. In other words, it is possible to develop antitoxic sera which will specifically neutralize the toxins produced by these bacteria. But it is extremely difficult to produce any real bactericidal antibodies by vaccination with the organisms themselves or the inoculation of any of their products. Dr. Dochez, who was one of the first to produce an antitoxin for the toxic filtrates of the streptococcus of scarlet fever, has been unable to produce an antibacterial serum. Dr. Park and his staff have likewise been baffled in the attempt to produce a serum which will combat the invasive properties of these organisms. Hopkins and Parker have been working on the same problem with staphylococcus and again although able to produce antitoxic sera which specifically neutralize the toxins of staphylococcus, they have not been able to produce a serum which affects in any way the invasive properties of that organism. Wright thought that by vaccination he could improve the opsonic index of patients and experimental animals and thus increase the resistance of the body to these infections. But these results have not

been confirmed and the technique of determining the opsonic index of serum even in experienced hands, has a large percentage of error. Although staphylococcus and streptococcus sera are made by several of the commercial firms and are used to a considerable extent by some practitioners who occasionally report extraordinarily good results of their use, in the hands of most critically minded doctors they have failed in the great majority of cases, as a survey of the subject reported in the recent medical literature indicated. I think that we may safely say that passive immunization with sera which are now available offers little hope of success in streptococcus and staphylococcus infections. One is justified however, in trying erysipelas serum in toxic cases of erysipelas. Anthrax antiserum has been used with real success in proven cases of anthrax and should always be used when it is available.

Very little can be said for active immunity. If it is impossible to produce a serum of any potency in experimental animals, it is equally difficult to produce it in man. The examination of the serum of patients who have survived an infection with these organisms, shows very little evidence of any protective substances. Even agglutinins or precipitins are frequently impossible to demonstrate in the serum. Giving vaccine during the course of an acute infection, or even a chronic one, is like adding fuel to flames. The only rationale of such treatment would be the theory that dead organisms or attenuated organisms injected into the normal tissues away from the lesion can produce protective antibodies which could be carried from the site of the inoculation to the site of the infection. This theory has not been satisfactorily substantiated by experimental proof. Vaccines have been used more extensively than sera in the treatment of such cases and have been given the credit for marvelous recoveries but there is little evidence that they were responsible for the cures. I have frequently prepared vaccines to be used in patients presenting a series of boils, and just at the time that I was about to begin their use, the patient showed evidence of recovery so that they were withheld. I have no doubt that in many

instances they have been administered under such conditions and have been given the credit for the cure which would have occurred quite as well without their use. The explanation of the failure of the body to produce effective protective antibodies against streptococcus and staphylococcus, is not understood. Dreyer believed that the tubercle bacillus could not be digested by the body down to the point where protective antibodies could be formed. He therefore suggested digesting the organisms outside of the body by means of trypsin or pepsin after the removal of the capsule by means of acetone. He believed that if the tubercle bacilli were digested down to just the right point and then injected, the body would be able to react to this split product of the organism and develop real protective antibodies against it. Dreyer's evidence was based upon insufficient experimental data, and other workers have not been able to confirm his results, as far as tuberculosis is concerned, but the theory may be sound and should be tested with other organisms. The studies which are now being made by Avery, Lancefield, Parker, Hopkins and others with regard to the antigenic properties of various fractions of the streptococcus and staphylococcus bodies may lead to the solution of this very important problem. Zinsser has stated that the size of a foreign protein molecule may be too large to enter the body cells. Before these cells can develop antibodies against that particular molecule of protein, it must be broken down until the size of the molecule may be sufficiently small to enter the cell. The difficulty of digesting streptococcus and staphylococcus with the usual proteolytic ferments is well known, and it may be that in these infections the ferments of the body are likewise unable to break down these proteins.

Besredka has attempted to overcome the difficulties of streptococcus and staphylococcus immunization by the use of bacterial filtrates, made from cultures in which the organisms have grown for some time. He has shown that the organisms do not grow in these filtrates and believes that they are exhausted as far as the nourishment requirement of the organisms is concerned, and more than that

contain an "antivirus" produced during the autolysis of the bacteria which helps to destroy organisms with which the filtrates come in contact. He advocates using these filtrates either by injection or application directly to the infected wound. Besredka's work has stirred up considerable controversy but his favorable reports have not been consistently confirmed by other workers.

Conclusion

When the patient gets well under treatment which we have found by experience to favor the recovery, we must realize that it is not the surgeon but the patient who overcomes the infection; the surgeon may turn the balance in favor of the patient by removing a large proportion of the bacteria and toxic products, and by improving circulation; when he relieves tension and applies heat. But after all, it is what goes on in the living tissues at the site of the lesion that determines whether there is to be recovery or further destruction. We know that patients recover from these infections and we assume that they have gained the upper hand by the development of some defense against the organism, but an examination of their blood serum fails to reveal any evidence of substances of a protective nature. Apparently the defense is purely a local one. The local tissues at the site of infection, develop a resistance which overcomes the invading organisms and which destroys most of them. After that it may be demonstrated that these tissues have a local immunity against further infection with the same organisms. Besredka demonstrated this and he found that the defense is a specific one, so that it is not merely the congregation of wandering cells but the adaptation of tissue cells which has occurred during the course of the infection which has enabled them to overcome the infection.

Acute infections may be divided into three groups, from the point of view of recovery. The first group includes those cases which recover without treatment or in spite of bad treatment. In another group the patients fail to re-

cover and die even though the best treatment that we know is applied promptly. The third group consists of those whose prompt recovery and cure depend upon the right treatment at the proper time. It is in these latter two groups that we are striving for an improvement in our results; for the former group to bring into the field of recovery those who now die in spite of the best treatment that we know; and for the latter group to increase the knowledge of both the patient and doctor, so that the best available treatment may be administered at the best time.

JOHN S. BROWNNE
1854-1931

JOHN S. BROWNNE

JOHN S. BROWNNE, Librarian and later Consulting Librarian to The New York Academy of Medicine, died at his home Haworth, New Jersey, February 27, 1931, aged seventy-six years.

The ending of this long and honorable career marks a notable event in the history of the institution to which, for nearly half a century, he contributed the full interest and endeavor of his life.

The Academy of Medicine, to-day in the full vigor of its well-developed prime, is the outcome of the earnest and intelligent efforts of many generations of able and devoted men, carried forward unremittingly for eighty years. As a factor in its progress the part contributed by Mr. Brownne was an all-important element. Our debt to him is great and lasting.

Thirty-five years after the founding of the Academy it had attained an importance which demanded a permanent home, properly equipped and managed for the effectual carrying out of its ever increasing affairs; since these had come to require more time and attention than any, even of its most self-sacrificing members, could afford, the services of a professional Librarian and General Superintendent had become imperative. When, in 1875, possession was taken of its first permanent home, in 31st Street, its far-sighted officers soon recognized the possibilities of its expansion and the necessity for its efficient management and, after long deliberation, from among thirty promising applicants whose qualifications were carefully studied, a selection, in 1880, was made.

Since then, the history of the Academy has been intimately identified with the life experience of that one who proved so largely responsible for its steady growth and prosperity. Quietly, without a suggestion of

self interest or obtrusiveness, his influence was exerted for the upbuilding of our institution, with a singleness of purpose and a steadfastness of devotion for which it would be hard to find a parallel. To it, more than to any other individual factor, was due not only our material prosperity but, even more important, that spirit of harmony which attended the Academy's contemporary existence. The character and personality of the man invariably attracted the best of those who knew him, both of the medical profession and of the laity, here and everywhere. He gained not only their confidence and friendship but their unqualified support, on his own part encouraging where encouragement was helpful, aiding by wise suggestions when consulted and by his hearty co-operation in the execution of the work; knitting together the forces of good for the general strengthening of the whole. His influence, exerted with intelligence and often with rare diplomacy, together with complete knowledge of what had preceded, caused each administration to glide quietly into the next without friction and with no interruption to the routine. Men in ever succeeding groups came and went, each faithfully and efficiently accomplishing his individual task. The all-embracing work of Mr. Brownne was perennial.

In reviewing the life of Mr. Brownne we are not surprised to find that he came of an ancestry sterling in itself and well adapted to the development of the particular abilities by which he himself was characterized.

His grandfather, Charles Brownne, a ship builder by profession, came from England in 1788 and established a shipyard in New York City in 1800. He was commissioned by Robert Fulton to build the "Clermont," and thus became the maker of the first practical steamboat. Fulton, his warm friend, bequeathed to him his watch, now in the possession of the family.

His father, Robert H. Brownne, was Librarian of the fine collection of Robert L. Stuart, later President of the American Museum of Natural History, and of the Presbyterian Hospital. He was also secretary to the North West-

ern Dispensary and was secretary and Librarian of the New York Lyceum of Natural History, the most influential scientific society of its time, itself an Academy in the highest acceptance of the word. Its membership included men of distinction in various departments of learning, among them Dr. Torrey, the well known founder of the New York Botanical Society, as well as a group of leading physicians who, taking their inspiration from the successful methods of the Lyceum and following the example of the Academy of Medicine of Paris, conceived and developed our own Academy of Medicine.

His mother, Angeline Betts Ferris, daughter of Josiah S. Ferris, a prominent citizen of Peekskill, N. Y. was descended from Geoffrey Ferris who came from Leicestershire, England, in 1666, and settled in Watertown, Mass.

Mr. John S. Brownne himself was born in King Street, Greenwich Village, N. Y., December 14, 1854. His earliest instruction was gained at the then well known Scotch Presbyterian School on 15th Street, of which his father was the principal. Later he entered the Leggett School, preparatory for West Point, where, although otherwise highly successful, he did not pass the physical tests and instead of pursuing the intended career at once secured the position of assistant Librarian in the Astor Library where he remained for about three years. Of studious mind and realizing the value of collegiate advantages he continued his education far beyond the customary limit of the graduate in arts. Already familiar with the routine of library work when called to the Academy, and fully informed as to the hopes and ambitions of his sponsors, he envisioned the possibilities of the representative medical institution of the great metropolis, at the outset designated as its true "Medical Center," and entered upon his new duties with full appreciation of the magnitude of the enterprise and of his responsibility to it; and with the clearly expressed determination to create for the Academy the best Medical Library in the world. In this endeavor he had the enthusiastic support of the succeeding groups of officers of the institu-

tion, men who possessed the culture, knowledge and influence to bring about the desired results.

The selection of Mr. Brownne was particularly happy, for he was amply prepared for the position, besides giving abundant promise of development. The salary was meagre for a Librarian, not to mention his other activities, even in those days; but the recognition of his worth suggested the making of a life as well suited to his means as possible for him and for the efficient execution of his many duties. In the agreement made, it was expressly stipulated that he should have suitable living quarters in the building. Being thus provided Mr. Brownne promptly married Miss Julia Seaman, of an old family of Long Island, and in the many succeeding years lived happily with his family in an atmosphere of appreciation and of substantial help, the spirit of which is well expressed in the recent words of one of them: "You know it is not every one who has had the privilege and the honor of being born and brought up in the Academy of Medicine."

Thus he was enabled to devote all possible daytime to the Library itself and to the securing, training, and supervising of its personnel, with the advantage that the Librarian and Manager was always available, fulfilling his multiple duties during the prescribed hours in the Library, and in the evenings arranging for and superintending the conduct of the various meetings, often until late at night. Such long hours would seem to have left little time for other things, but in addition to them, when there were no meetings many of the evening hours were devoted by him to the book-keeping and other necessary details of the business and material management. By diligent pursuance of this routine, conducted with unfaltering zeal, the Academy flourished as only we who shared its history and worked earnestly in its behalf can know.

While recognizing the individual worth of Mr. Brownne's administration and according to him full credit for the many excellencies which he so well achieved, it must be remembered that in these things he enjoyed assistance

of far more than usual value. The Library Committees were carefully selected from among the very best of the earnest and cultured Fellows of the Academy, ever deeply interested in its welfare and ardent in their activities and their support.

The actual executive work was shared by the chief assistant librarian, Mrs. Laura E. Smith, a lady, thoroughly equipped in all that pertained to her position, who for thirty-five years a talented and devoted associate, was by all held in highest esteem.

To further the conduct of material affairs, a practical House Superintendent was needed, and was secured in the person of Mr. Felix Westrom, an efficient aid, and an invaluable adjunct to the general atmosphere and welfare. Thus was completed a working staff of unique character and efficiency, earnest of purpose, harmonious with one another, proud of the institution which they so loyally supported, and universally appreciated. These, throughout the long period of their activity, were the soul and spirit of the place, patiently but surely, with rare wisdom and tact, stimulating its progress and communicating to the entire personnel their self-contained enthusiasm.

With the diligent pursuance of their routine, conducted under the genial management of the Librarian-in-chief, the Academy increased rapidly in volume and importance. Desirable additions to it often appeared for sale, and in the competition for them he frequently out-bid powerful rivals, funds being provided by enthusiastic members or by their friends, in the acquiring of whose attention and generous interest Mr. Brownne was particularly successful. The most important acquisition came through the Governors of the New York Hospital, who, in 1898, donated to the Academy the Library of the New York Hospital, numbering 23,000 volumes, a fine collection founded in 1798, and during its last half century under the able direction of its Librarian, Mr. John L. Vandervoort.

This library included the celebrated collection of rare

old books on the history of medicine made by Dr. John Watson, which was the beginning of the Academy's present fine collection of incunabula, greatly valued by Mr. Brownne.

Year by year, with steady increase, the Academy gained. Its reliability was widely recognized, the dignity of its ambition approved, and its value utilized.

Books in considerable number were given by members, among whom was Dr. Purple, an ardent collector. For many years he had gathered complete files of American medical periodicals, until he had acquired the most nearly perfect series in existence. These he presented to the Academy.

Some years before the Academy moved into Thirty-first Street, Dr. Frank P. Foster, editor of the New York Medical Journal, had established a society known as the Medical Journal Association, which had its quarters in 1871 at the Mott Memorial, 64 Madison Avenue, and in 1874 in the building 107 East Twenty-eighth Street, at that time as now occupied by Tiemann and Company. By a friendly arrangement the Journal Association was merged into the Academy, where it at once created for the institution its department of current periodicals.

The growth of the Library, according to the record, eloquently testifies to the character and value of Mr. Brownne's stewardship. On his accession, in 1880, the total number of books was 25,000; upon his retirement in 1926, there were 139,320 books, 98,685 pamphlets and journals subscribed for, making a total of 239,505 titles, in itself alone a splendid fulfillment of his original ambition.

Among many collateral services assumed by Mr. Brownne and suggestions made by him, were several of permanent importance. Not seldom, following the death of various prominent physicians, their widows would apply to him for advice as to the disposal of their collections of books and instruments, often representing the interests of a lifetime. Books of value not already owned by the

Academy were purchased by him; the rest were referred to places where they could be disposed of to advantage. The same course was pursued with the instruments. Among them some were valuable because of original design or of antiquity; others representing old forms, long since disused but having belonged to some distinguished man. These were carefully preserved by Mr. Brownne, with the often expressed intent of establishing with them a museum; an idea now being successfully elaborated.

Upon the removal to 43rd Street Mr. Brownne inaugurated a Department of Exchange. This soon became an important feature, widely appreciated and utilized. Gifts to other libraries since then have been continuous and there are few which have not received substantial help from the duplicate and triplicate service established. Many boxes were carefully packed by Mr. Brownne himself in the basement of the building where most of that material was stored, amid inconvenient conditions.

At the time of the great earthquake in Japan the Medical Library at Tokio was destroyed. Mr. Brownne at once busied himself in doing all possible to form a new one and thus without delay to further the uninterrupted progress of medical education. His efforts were successful, for he sent what was virtually a complete equipment. In many other instances the same was done, notably in that of the Lane Library, destroyed in the San Francisco disaster of 1906.

Upon his retirement from active direction Mr. Brownne was made Consulting Librarian, residing at Haworth, New Jersey, not far from his two married daughters. With his wife and with them and their families, including two fine grandsons, he enjoyed the quietude of his own home, where among his flowers and books the subsequent years were passed. His health had been impaired by reason of his unremitting activities, and about two years ago it was discovered that his heart was seriously affected. The outlook was unfavorable, but under skillful treatment his life was prolonged far beyond expectation. Weakened

by long-continued over-use of the eyes, he also developed glaucoma, which was operated upon; but subsequently inoperable cataract appeared. He had long wished to write a History of Medicine, especially as relating to New York and more particularly to The New York Academy of Medicine—the latter's influence upon medicine in general and its special influence during the years of his administration. This, unfortunately became impossible on account of failing eyesight and his general physical condition. The loss of his observations upon these events, as well as upon the characteristics of those he had met so intimately among the great ones of that era is irreparable. He had accumulated a mass of material upon the subject, which is preserved.

At the close of his illness and during the last days of his life, surrounded by his family and in the natural clouding of the mind which attended his condition, he constantly recurred to the subject of the library, its books, and the friends who had been his constant companions there, evidently happy in his thoughts of them and in the nearer memories of his well-rounded life.

The record of the Academy during Mr. Brownne's administration was one of steady, uninterrupted advancement, as he had hoped from the beginning. There was no retrogression, nor, from the day of its founding any suspension of its varied activities. With every season these became broader and more indispensable until, with the progress which was demanded by vastly increased detail and more generous space and adequate service, the expansion which had become imperative was met, and the present building inaugurated.

Successfully emerging from the early struggles of its birth and childhood, the Academy had been committed to the care of our friend, who cherished and guided the period of its ever growing youth until, crowning his well accomplished life-work, it was passed on to his successors, amply prepared to advance in the full strength and courage of splendid maturity.

The varied nature of Mr. Brownne's interest demonstrates the breadth of his character and mind. He was an Honorary member of the New York Historical Society and of the New York Academy of Sciences. He was, also, a member of the American Association of Medical Librarians, at one time chairman of its executive committee; of the Sons of The Revolution and of various other societies of art and of science.

He was an Elder in the Park Presbyterian Church, New York, and a Republican. His favorite recreations were fishing, hunting and horseback riding.

DAVID BRYSON DELAVAN.

RECENT ACCESSIONS TO THE LIBRARY

Asch, P. Die moderne Therapie der Gonorrhöe beim Manne. 3. Aufl.
Berlin, Marcus, 1930, 91 p.

Aschner, B. Klinik und Behandlung der Menstruationsstörungen.
Stuttgart, Hippokrates-Verlag, 1931, 488 p.

von Bälz, E. Erwin Bälz; das Leben eines deutschen Arztes in erwachenden Japan.
Stuttgart, Engelhorn, 1931, 454 p.

Berg, R. Eiweissbedarf und Mineralstoffwechsel bei einfachster Ernährung.
Leipzig, Hirzel, 1931, 239 p.

Bourne, G. An introduction to medical history and case taking.
Edinburgh, Livingstone, 1931, 195 p.

Camino Galicia, J. Psiquiatria general. Delirios y delirantes.
Madrid, Saez, 1930, 203 p.

Chabanier, H. E. L. and Lobo-Onell, C. Exploration fonctionnelle des reins.
Paris, Masson, 1930, 569 p.

Chittenden, R. H. The development of physiological chemistry in the United States.
N. Y., Chemical Catalog Co., 1930, 427 p.

Coburn, A. F. The factor of infection in the rheumatic state.
Balt., Williams, 1931, 288 p.

Faber, K. H. Nosography; the evolution of clinical medicine in modern times. 2. ed.
N. Y., Hoeber, 1930, 222 p.

Garrod, (Sir) A. E. The inborn factors in disease.
Oxford, Clarendon Press, 1931, 160 p.

Gesell, A. The guidance of mental growth in infant and child.
N. Y., Macmillan, 1930, 322 p.

Glénard, R. Réactions vaso-motrices du foie en clinique.
Paris, Doin, 1931, 239 p.

Gini, C.; Boldrini, M.; de Berardinis, L. [et al.] Demografia.
Torino, Unione Tipografico-Editrice Torinese, 1930, 740 p.

Guiard, E. La trépanation cranienne chez les néolithiques et chez les primitifs modernes.
Paris, Masson, 1930, 126 p.

Halliburton, W. D. and McDowall, R. J. S. Handbook of physiology. 19. ed.
London, Murray, [1930], 842 p.

Hapgood, R. L. History of the Harvard Dental School.
Boston, Harvard Univ. Dent. School, 1930, 343 p.

Hertzler, A. E. Surgical pathology of the diseases of bones.
Phil., Lippincott, [1931], 272 p.

Holmes, G. W. and Ruggles, H. E. Roentgen interpretation. 4. ed.
Phil., Lea, 1931, 339 p.

Houstoun, R. A. A treatise on light. [6. ed.].
London, Longmans, 1930, 494 p.

Humphris, F. H. and Stuart-Webb, R. E. Physiotherapy.
London, Cape, [1930], 384 p.

Isaacs, S. Intellectual growth in young children.
N. Y., Harcourt, 1930, 370 p.

Jung, C. G. Psychologische Typen.
Zürich, Rascher, [1930], 724 p.

Kilduffe, R. A. The clinical interpretation of blood examinations.
Phil., Lea, 1931, 629 p.

Kirk, J. B. Public health practice in the tropics.
London, Churchill, 1931, 498 p.

Klotz-Guérard, J. La thérapeutique par voie nasale.
Paris, Les Presses Universitaires de France, [1930], 158 p.

Lebensproblem (Das) im Lichte der modernen Forschung. Hrsg. von H. Driesch.
Leipzig, Quelle, 1931, 461 p.

Lockyer, C. H. J. The Lockyer collection of obstetric and gynaecological specimens.
London, Bale, 1930, 297 p.

Menge, E. J. v. K. A survey of national trends in biology.
Milwaukee, Bruce, [1930], 156 p.

Miller, E. Modern psychotherapy.
London, Cape, [1930], 131 p.

Mühl, A. M. Automatic writing.
Dresden, Steinkopff, 1930, 214 p.

Neuburger, M. Essays in the history of medicine.
N. Y., Medical Life Press, 1930, 210 p.

Osgood, E. E. and Haskins, H. D. A textbook of laboratory diagnosis.
Phil., Blakiston, [1931], 475 p.

Perutz, A. Allgemeine Therapie der Hautkrankheiten.
Wien, Springer, 1930, 123 p.

Peter, L. C. The principles and practice of perimetry. 3. ed.
Phil., Lea, 1931, 315 p.

Pincussen, L. Photobiologie; Grundlagen, Ergebnisse, Ausblicke.
Leipzig, Thieme, 1930, 543 p.

Piney, A. Recent advances in haematology. 3. ed.
London, Churchill, 1931, 348 p.

Preventive management: mental hygiene in industry. Edited by H. B. Elkind.
N. Y., Forbes, [1931], 234 p.

Pryde, J. Recent advances in biochemistry. 3. ed.
London, Churchill, 1931, 393 p.

de Quervain, F. Spezielle chirurgische Diagnostik. 9. Aufl.
Leipzig, Vogel, 1931, 916 p.

Rackemann, F. M. Clinical allergy, particularly asthma and hay fever.
N. Y., Macmillan, 1931, 617 p.

Rood, F. S. and Webber, H. N. Anaesthesia and anaesthetics.
N. Y., Wood, 1930, 292 p.

Saunders, J. T. and Manton, S. M. A manual of practical vertebrate morphology.
Oxford, Clarendon, 1931, 220 p.

Scherber, G. Beiträge zur Lösung des Krebsproblems.
Wien, Perles, 1930, 158 p.

Schürmann, P.; Pflüger, H. and Norrenbrock, W. Die Histogenese ektomesodermaler Mischgeschwülste der Mundhöhle.
Leipzig, Thieme, 1931, 94 p.

Seemann, G. Histobiologie der Lungenalveole.
Jena, Fischer, 1931, 88 p.

Socialization (The) of medicine. Compiled by Edith M. Phelps.
N. Y., Wilson, 1930, 190 p.

Still, G. F. The history of paediatrics.
London, Milford, 1931, 526 p.

Tarugi, N. Trattato di chimica bromatologica.
Milano, Vallardi, 1930, 460 p.

Terrill, H. M. and Ulrey, C. T. X-ray technology.
N. Y., Van Nostrand, 1930, 256 p.

Trial of Frederick Guy Browne and William Henry Kennedy.
Edinburgh, Hodge, [1930], 218 p.

Vidal Jordana, G. Trastornos nutritivos del lactante.
Barcelona, Marín, 1930, 288 p.

Walscheid, A. J. Abdomino-pelvic diagnosis in women.
St. Louis, Mosby, 1931, 1000 p.

Wickes, (Mrs.) F. G. The inner world of childhood.
N. Y. Appleton, 1930, 379 p.

Young, J. K. Handbook of anatomy. 7. ed.
Phil., Davis, 1930, 460 p.

PROCEEDINGS OF ACADEMY MEETINGS

APRIL

Stated Meetings

Thursday Evening, April 2, at 8:30 o'clock

Program presented in coöperation with the

Section of Medicine

and the

New York Gastro-Enterological Society

I. Executive Session

Election of Fellows

II. Papers of the Evening

a. The mechanism of gastric secretion, B. P. Babkin, McGill University (by invitation)

b. The motor mechanism of the large bowel, A. J. Carlson, University of Chicago, Department of Physiology (by invitation)

Discussion, Martin E. Rehfus, Philadelphia (by invitation), Leon T. LeWald, John L. Kantor, Albert F. R. Anderson

III. Executive Session—Section of Medicine

Nomination of officers and one member of advisory committee

Thursday Evening, April 16, at 8:30 o'clock

The Seventh Harvey Lecture

"The Use of Cold in the Analysis of Physiological Function"

Sir William Hardy

Food Investigation Board

of the

Department of Scientific and Industrial Research

and

Low Temperature Research Station

Cambridge, England

Alfred E. Cohn, President, Harvey Society

Dayton J. Edwards, Secretary, Harvey Society

Section Meetings

Section of Surgery

Wednesday Evening, April 1, at 8:30 o'clock

(Please note change in date)

ORDER

I. Reading of the Minutes

II. Presentation of Cases

a. Splenectomy for purpura hemorrhagica, Edward J. Donovan

b. 1. Meningocele—6 years after operation

2. Spina bifida—6 years after operation

3. Mesenteric thrombosis—intestinal resection—2 years after operation, Irwin E. Siris

c. Two cases demonstrating a method of removing a semilunar cartilage of knee joint, Russel H. Patterson

III. EXECUTIVE SESSION

a. Nomination of officers and one member of Advisory Committee

b. Report of committee on proposed new classification of membership in the Academy and qualifications for Fellowship in Surgery

c. Discussion opened by John A. Hartwell

SECTION OF DERMATOLOGY AND SYPHILOLOGY

Tuesday Evening, April 7, at 8:30 o'clock

ORDER

I. EXECUTIVE SESSION

a. Reading of the Minutes

b. Nomination of officers and one member of Advisory Committee

II. PRESENTATION OF CASES

a. Cases from Skin and Cancer Hospital

b. Miscellaneous cases

III. GENERAL DISCUSSION

SECTION OF PEDIATRICS

Thursday Evening, April 9, at 8:30 o'clock

ORDER

I. EXECUTIVE SESSION

Nomination of officers and one member of Advisory Committee

II. PAPERS OF THE EVENING

The breathing of normal new born infants, Douglas Murphy, Philadelphia (by invitation)

Discussion opened by Walter Lester Carr

III. The treatment of convulsant poisons with the aid of the Drinker respirator, Joseph Stokes, Philadelphia (by invitation)

Discussion opened by Henry B. Wightman (by invitation)

IV. Congenital heart disease, clinical analysis of 82 cases with autopsy findings, Clifton B. Leech, Providence (by invitation)

Discussion opened by Clarence de La Chapelle, Charles Hendee Smith

SECTION OF NEUROLOGY AND PSYCHIATRY

Tuesday Evening, April 14, at 8:30 o'clock

ORDER

I. EXECUTIVE SESSION

a. Reading of the Minutes

b. Nomination of officers and one member of Advisory Committee

II. CLINICAL PRESENTATIONS

a. An initial visit, Philip R. Lehrman

b. Complementary neurosis in a married couple, Clarence P. Oberndorf

III. PAPER OF THE EVENING

The present status of psychoanalysis as a psychologic and therapeutic system, Franz Alexander, Visiting Professor of Psychoanalysis, University of Chicago (by invitation)

Discussion, J. Ramsay Hunt, Smith Ely Jelliffe, A. A. Brill

IV. General Discussion

Section of Genito-Urinary Surgery

Wednesday Evening, April 15, at 8:30 o'clock

ORDER

I. Executive Session
   a. Reading of the Minutes
   b. Nomination of officers and one member of Advisory Committee

II. Presentation of Cases
   a. Kidney lesion simulating solitary cyst, Paul W. Aschner
   b. Cyst of the prostate, Allen M. Margold (by invitation)
   c. Radical operation for carcinoma of the penis, Herbert Willy Meyer

III. Papers of the Evening
   a. The surgical treatment of nephritis, Irving Simons
   b. The use of surgical endothermy in suprapubic prostatectomy, Paul W. Aschner

   Discussion, J. Sturdivant Read

IV. General Discussion, Joseph McCarthy, Oswald Lowsley, Paul Aschner, Leon T. Le Wald, Leo L. Michel

Section of Ophthalmology

Monday Evening, April 20, at 8:30 o'clock

ORDER

I. Executive Session
   a. Reading of the Minutes
   b. Nomination of officers and two members of Advisory Committee

II. Presentation of Cases
   a. A case of voluntary nystagmus, Hugh S. McKeown (by invitation)
   b. 1. An operation for epiphora
      2. Subconjunctival hemorrhage as a diagnostic sign in intraocular foreign bodies, Benjamin Friedman (by invitation)

III. Demonstrations
   a. An abbreviated method of muscle resection, Sigmund A. Agatston
   b. The development of the cornea in the chick embryo, George F. Laidlaw

IV. Paper of the Evening

   Significant hemorrhagic retinal lesions occurring in bacterial endocarditis—Roth's spots (lantern slides), William Brown Doherty, Max Trubek (by invitation)

   Discussion, Alexander Lambert, Emanuel Libman

V. General Discussion

Section of Medicine

The regular meeting was not held on April 21 for the reason that the Section of Medicine and the New York Gastro-Enterological Society presented the Stated Meeting of April 2.

JOINT MEETING
of the
SECTION OF OTOLOGY
and the
SECTION OF LARYNGOLOGY AND RHINOLOGY
Wednesday Evening, April 22, at 8:30 o'clock

ORDER

I. EXECUTIVE SESSION
   a. Nomination of officers and one member of Advisory Committee
   b. Report of Advisory Committee on proposed new classification of membership in the Academy and qualifications for Fellowship in Otology and Rhino-Laryngology
   c. Consolidation of the Section of Otology and the Section of Laryngology and Rhinology
II. PAPERS OF THE EVENING
   SYMPOSIUM ON "PNEUMOCOCCIC AND STREPTOCOCCIC MENINGITIS"
   a. Otological aspect, James G. Dwyer
   b. Rhino-laryngological aspect, Lee M. Hurd
   c. Prophylaxis and treatment, John A. Kolmer, Research Institute of Cutaneous Medicine, Philadelphia (by invitation)
   Discussion opened by Andrew A. Eggston, Ira Cohen, Samuel J. Kopetzky

SECTION OF ORTHOPEDIC SURGERY
Friday Evening, April 24, at 8:30 o'clock
(Please note change in date)

ORDER

I. EXECUTIVE SESSION
   a. Reading of the Minutes
   b. Nomination of officers and one member of Advisory Committee
II. PAPERS OF THE EVENING
   a. The operative treatment of hallux valgus, Samuel Kleinberg
   b. A simple and effective method of bone suture, especially applicable to the bones of the forearm, Isadore Zadek
   c. Therapeutic and physical properties of ultraviolet irradiation of petrolatum, Eugene H. Eising
III. GENERAL DISCUSSION

SECTION OF OBSTETRICS AND GYNECOLOGY
Tuesday Evening, April 28, at 8:30 o'clock

ORDER

I. READING OF THE MINUTES
II. PAPERS OF THE EVENING
   a. The value of external cephalic version in transverse and breech presentations, Oskar Glassman (by invitation)
   Discussion opened by G. H. Ryder, Abraham J. Rongy, Samuel J. Scadron, Hervey C. Williamson

b. The Elliott treatment in pelvic inflammation, Frederick C. Holden, Emily D. Barringer, Henry C. Falk, Max S. Rohde, Mortimer N. Hyams, Robert Gutierrez

c. Computation and standardization of the maternal mortality rate, R. J. Lowrie (by invitation)

III. General Discussion

IV. Executive Session

a. Nomination of officers and one member of Advisory Committee

b. Discussion of the qualifications for Fellowship in the Section of Obstetrics and Gynecology.

Society for Experimental Biology and Medicine

Under the auspices of

The New York Academy of Medicine

Monday, April 20, at 5 o'clock

Annual Scientific and Business Meeting

I. A Method for Preparing an Active Adrenal Cortex Extract, R. L. Zwemer, F. J. Agate, Jr., and H. A. Schroeder (introduced by P. E. Smith)

II. A Blood-Chemical Test for Adrenal Cortex Extracts, R. L. Zwemer and R. C. Sullivan (introduced by P. E. Smith)

III. Continuous Pancreatic Secretion, B. N. Berg and T. F. Zucker

IV. Antagonistic Action Between Parathormone and Irradiated Ergosterol in Experimental Fibrous Osteodystrophy of Guinea Pigs, A. J. Abeloff and I. P. Sobel (introduced by E. H. Fishberg)

V. Action of Thyroxin on Tissue Metabolism, Aleita Hopping (introduced by E. L. Scott)

VI. Effect of Adrenal Cortical Hormone upon Respiratory Metabolism of Adrenalectomized Cats, W. W. Swingle, J. J. Pfiffner and B. Webster

VII. Solubility of Human Gall Stones in Dog Bile, L. Bauman and G. O. Spanner

VIII. Amino Acids as the Only Nitrogen Source During Growth and Differentiation, O. Hoffman and F. Gudernatsch (introduced by A. J. Goldforb)

IX. Pharmacology of Ruvettus pretiosus, or "Castor-Oil Fish," D. I. Macht and J. Barba-Gose

X. Production of anatomical lesions in the isolated organ, Jean R. Oliver

Please note change of date of meeting to Monday, April 20, at 5 p. m. Dinner to follow.

Peyton Rous, President

A. J. Goldford, Secretary

THE NEW YORK ROENTGEN SOCIETY
In Affiliation with
THE NEW YORK ACADEMY OF MEDICINE
Monday Evening, April 20

ORDER

I. 8:30 P. M.
Demonstration of interesting cases and roentgenograms
II. 9:00 P. M.
a. Some roentgenological lesions in the long bones of growing individuals in clinical and experimental poisoning by lead
b. The roentgenological changes in the bones in the hemolytic changes in childhood; a clinical and roentgenological correlation
c. Roentgenograms of interesting cases from the Babies' Hospital, John Caffey
III. GENERAL DISCUSSION
To be opened by Leopold Jaches, Nathan Rosenthal
IV. EXECUTIVE SESSION
ROSS GOLDEN, President
J. BENNETT EDWARDS, Secretary

NEW YORK PATHOLOGICAL SOCIETY
In Affiliation with
THE NEW YORK ACADEMY OF MEDICINE
Thursday Evening, April 23, at 8:30 o'clock

ORDER

I. PRESENTATION OF PAPERS
a. Two unusual heart lesions, Max Lederer
b. A case of endocarditis due to Bacillus acidi lactici, Lewis Dickar (by invitation)
c. The pathology of Bartonella muris anemia, J. Marmorston-Gottesman (by invitation), David Perla
d. The compensatory phenomena following splenectomy in albino rats, David Perla, J. Marmorston-Gottesman (by invitation)
II. EXECUTIVE SESSION
LEILA C. KNOX, President, St. Luke's Hospital
BERYL H. PAIGE, Secretary, The Babies' Hospital

FELLOWS ELECTED MAY 7, 1931

Julius Arnowich.....200 West 111 Street
Gordon M. Bruce .....180 Ft. Washington Avenue
Henry G. Bullwinkel.....30 East 76 Street
Alvin F. Coburn.....622 West 168 Street
Charles W. Depping.....17 West 54 Street
Emil A. Falk.....44 East 76 Street
Philip Finkle.....1185 Park Avenue
Clarence C. Fuller .....565 Park Avenue
Sol W. Ginsburg.....39 West 55 Street
Arnold Koffler.....302 West 86 Street
Laura Miller.....17 West 54 Street
Pro. V. Prewitt.....885 Park Avenue
Fred H. Voss.....69 Spring Street, Kingston
Siegfried Wachsmann .....565 Manhattan Avenue
Preston A. Wade.....1045 Park Avenue

DEATHS OF FELLOWS OF THE ACADEMY

Herman Arthur Haubold, M.D., 22 West 9th Street, New York City; graduated in medicine from Bellevue Hospital Medical College, New York City, in 1889; elected a Fellow of the Academy February 4, 1897; died, May 5, 1931. Dr. Haubold was a Fellow of the American Medical Association, a member of the County and State Medical Societies, a member of the Society of Alumni of St. Vincent's Hospital and Consulting Surgeon to Harlem, Broad Street, Nassau and Mineola Hospitals, New York, also to the Memorial Hospital, New London, Connecticut.